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VOLUME 20
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American Journal of Diseases of Children

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REPORT ON A CASE OF MALIGNANT THYMOMA WITH NECROPSY *

NATHAN CHANDLER FOOT, M.D.
BOSTON

One does not often encounter malignant tumors of the mediastinum and it is seldom that they are to be procured in as fresh a state of preservation as that which I shall report:

REPORT OF CASE

Case.—The patient, G. S., aged 9 years, was sent in to the service of Dr. James S. Stone, in the Children's Hospital, from a suburban hospital April 30, 1919, with the diagnosis of mediastinal tumor.

Previous History.—He was a normally delivered, full-term child, with a negative family history. Ever since his fourth year be had had frequent attacks of tonsillitis, which led to the removal of his tonsils and adenoids when he was 6 years old. During the winter months he had frequent colds and coughing which usually lasted two to three weeks at a time; these would occur as often as every month.

Present Illness.—His present illness began with a gradual onset of coryza and inspiratory dyspnea, one month prior to admission. He could not lie flat in bed, having well marked orthopnea. Two weeks after onset, his mother noticed swollen veins at the base of his neck, just above the clavicle. She stated that roentgen-ray examination at the local hospital was negative. The patient was better at the time of his admission to the Children's Hospital, able to lie flat and sleep on one pillow; he had occasional fits of gagging and coughing, which would awaken him at night, but was otherwise pretty comfortable. He did not raise much, if any, mucus when he coughed, there was no cyanosis, no convulsions, no bleeding from the nose or the mouth. He had no pain in his chest, no night sweats or night cries.

Physical Examination.—There was dullness on both sides of the sternum from the first to the fifth rib, breath sounds and voice sounds were increased; there was bronchovesicular breathing. Breath sounds were more nearly normal on the left than on the right side. There was a dor[illegible] scoliosis of the spine to the right. The patient was round-shouldered. The heart sounds were clear and normal; precordial dullness measured 2.5 by 8.5 cm. The aortic second sound was louder than the pulmonic second. The abdomen was negative. The extremities were of equal size with veins showing prominently in places. Blood pressure, left: 130 mm.; right: 120 mm.

Roentgen-Ray Examination.—This showed (Fig. 1) a large mediastinal tumor, occupying the upper central portion of the chest; stereoscopic roentgenograms showed that it was anterior to the great vessels. The veins in the anterior and lower part of the neck were prominent, and there was slight enlargement of the veins of the upper part of the chest anteriorly.

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* From the pathological laboratory of the Children's Hospital, Boston, Mass., and the Department of Pathology, Harvard Medical School, Boston, Mass.

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Laboratory Findings.—The urine was normal. Leukocytes, 12,000; erythrocytes, 4,460,000. Differential count: Polymorphonuclears, 69 per cent.; mononuclears, 31 per cent. The blood smear showed nothing abnormal. Hemoglobin, 90 per cent. The von Pirquet test was negative. Except for two rises in temperature to 99 on the days he was roentgenographed, the temperature curve was comparatively flat.

Diagnosis.—A tentative diagnosis of mediastinal abscess or enlarged mediastinal nodes was made on admission.

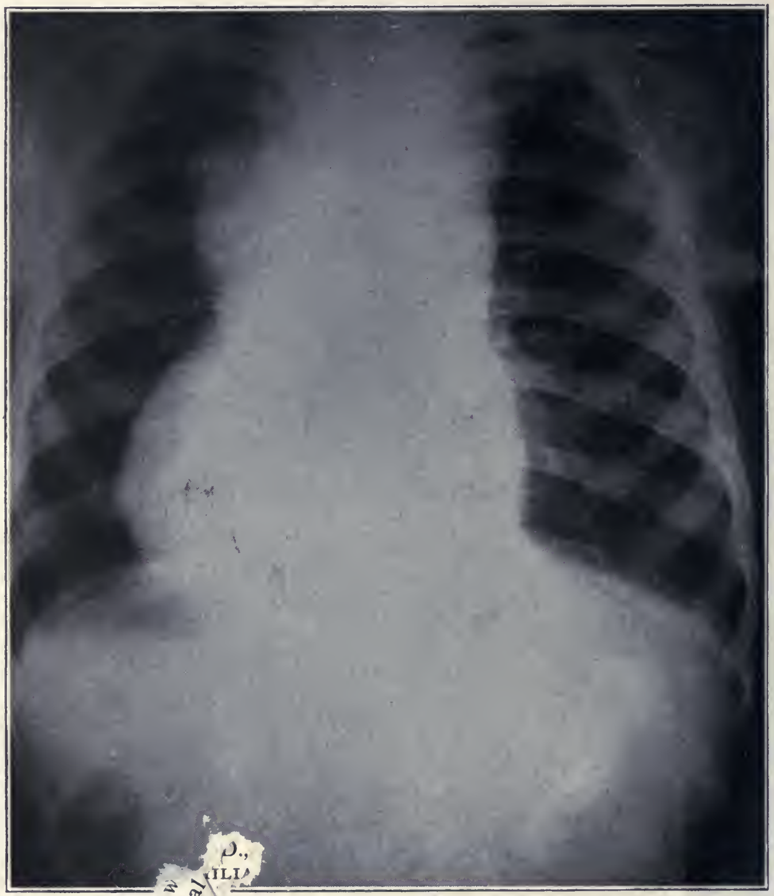

Fig. 1.—Roentgenogram of tumor, taken during life by Dr. Percy Brown.

Operation.—The patient was taken to the operating room one week after admission, for the purpose of making an exploration. He took his ether well, holding the cone himself, until partially anesthetized. As the anesthesia became complete he grew markedly cyanotic and the ether was immediately stopped, the usual restoratives, including oxygen being used. The boy's color improved steadily and became almost normal. His heart seemed to be in good condition. He never regained consciousness, however, and one-half hour after starting anesthesia he suddenly became very pale, and his heart and respiration stopped abruptly. Tracheotomy was not performed, as there was no hope of relieving the obstruction by this means. A necropsy was performed four hours later.

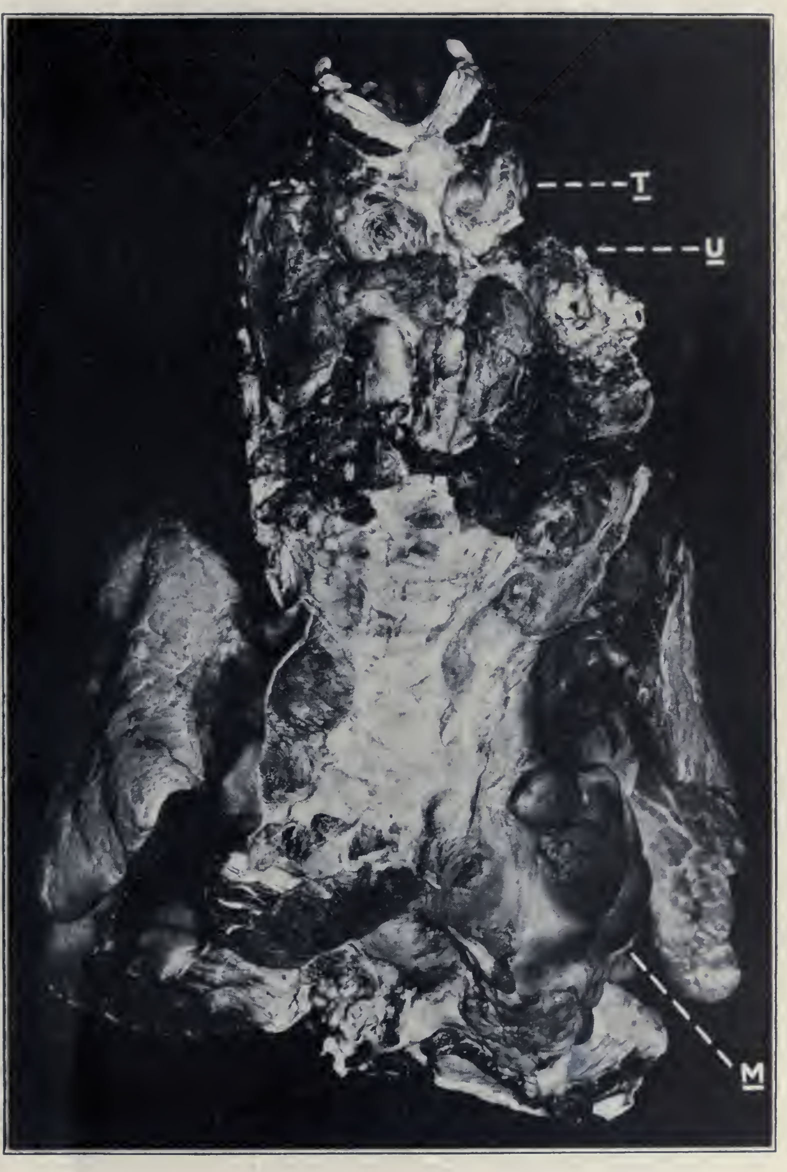

Fig. 2.—The tumor viewed from in front. T = thyroid gland; U = upper limit of tumor; M = metastases into pericardium, which is unopened. Lungs on either side.

Necropsy Report.—The body is that of a well nourished, well developed, white male child, 139 cm. in length. There is no rigor mortis, except in the lower jaw; postmortem lividity is present in dependant portions. There is nothing remarkable about the head. A bulging mass is palpable above the suprasternal notch, extending as high as the thyroid and firm and lobulated. The left side of the thorax is noticeably arched and protruding; otherwise not externally abnormal. Primary incision, extending from suprasternal notch to mons pubis. The abdominal contents are in situ, but there are adhesions between the gallbladder and pylorus and the transverse colon and liver. The intestines as a whole, are congested. There is a small accessory spleen, 1.2 cm. in diameter, situated just off the lower pole of the spleen proper and about 1.5 cm. distant therefrom. The liver projects 1.5 cm. below the free margin of the ribs. The mesenteric lymphnodes are all enlarged, some of them to 2 cm. in diameter. They show coarse, whitish follicles through their capsules and the largest of them is almost completely caseous. The diaphragm is at the first rib on the right, at the fifth interspace on the left. On opening the thorax one notes that the costal cartilages cut easily and that the muscles covering the thorax are of good color. On removing the sternum, a tumor of very extensive growth is encountered.

This tumor lies in the anterior mediastinum, is adherent to, but does not infiltrate the sternum and extends from the thyroid gland above to the diaphragm below. The organs of the neck and thorax were removed in toto, in order that they might be studied more intelligently. The pericardium contains 200 c.c. of clear, straw colored fluid; its inner surface is studded with small, granular tumor masses; its outer aspect shows several large infiltrating masses of tumor tissue, about 2 cm. in diameter and 0.75 cm. in thickness, as shown in Figure 2. The heart is firmly contracted and shows small masses of a similar nature on its epicardium, varying from 1 mm. to 1.3 cm. in diameter and penetrating the myocardium to a slight extent.[1] The lungs show no internal abnormalities on section, although there are metastatic foci in the pleura. For the sake of coherence, the tumor will be described later, its gross and microscopic peculiarities being combined.

Abdomen: The spleen is very firm, purplish red and weighs 101 gm. On section, it drips bloods, its pulp is firm and does not strip readily on the knife blade. The splenic corpuscles are coarse and prominent, whitish in color; the trabeculae are normal in size and number. The organ contains one small metastatic nodule, spherical in shape and cartilaginoid in consistence. It is yellowish white and measures 0.5 cm. in diameter.

Liver: Weight, 830 gm. It is dark reddish brown in color, mottled with a definite nutmeg pattern. Its capsule is everywhere smooth and glistening, except where there are adhesions with neighboring viscera. At the apex of its convex surface, near the middle of the falciform ligament and to the right of it, is a spherical mass, yellowish white and 1.2 cm. in diameter. It is very firm in consistence. On the under surface of the left lobe is another such mass, stellate in outline and 1.5 cm. in diameter, which is completely calcified. The cut surface of the liver drips blood, is finely patterned in a nutmeg design of reddish brown and seems not unduly fibrous or greasy. The gallbladder contains viscous, olive green bile which is readily expressed through the papilla of Vater.

Stomach: This organ is of normal size, its mucosa velvety and of the usual appearance; there is marked congestion and a large hemorrhagic erosion in the duodenum, just below the pylorus. It is 2.5 cm. in diameter; the mucosa is ulcerated and there is evidence of fresh hemorrhage here. Some bloody mucus lies in the lumen of the gut. The intestines show similar areas of hemorrhage here and there and they are congested, as a whole, the congestion being apparently passive in type. Pancreas: This is of normal size and consistence. Kidneys: They weigh together 218 gm. Their capsules strip readily, exposing a smooth surface, with injected stellate venules. The organs show congestion on cutting them open, are of a dark red color, drip blood and the congestion is apparently of a passive type, similar to that in the other organs. The ratio of medullary to cortical diameter is normal, there is nothing abnormal about the pelves, ureters, nor urinary bladder.

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[1] Grawitz: Deutsch. med. Wchnschr. **37**:2357, 1911.

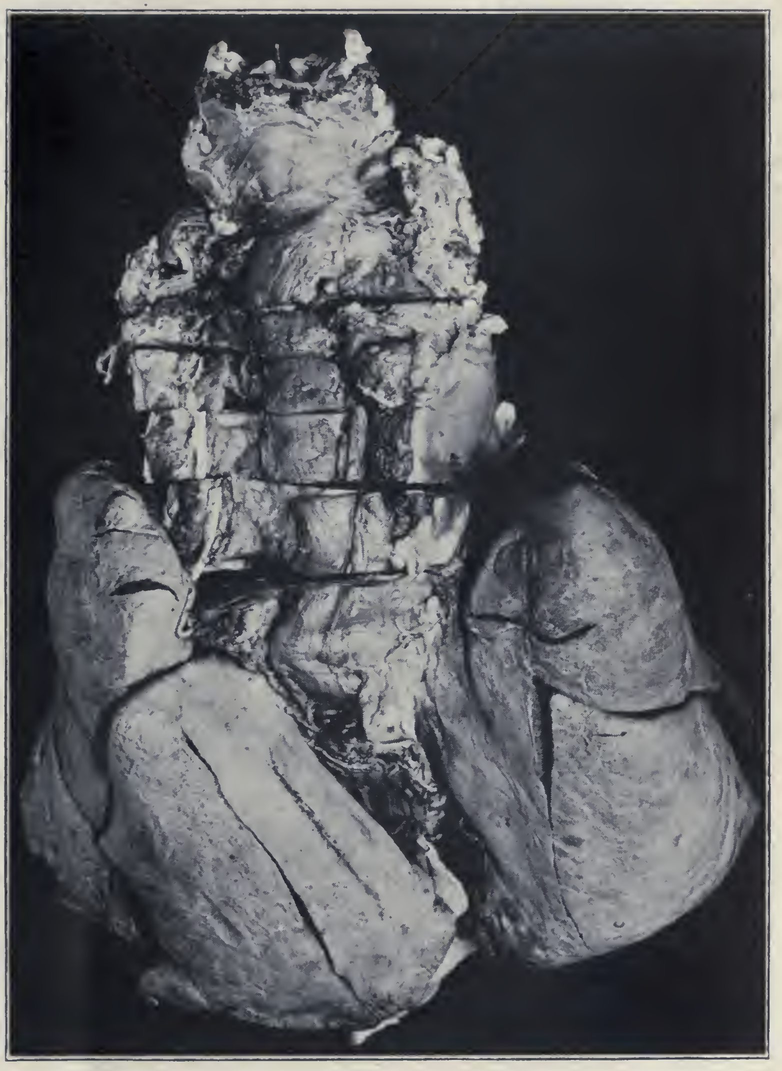

Fig. 3.—The tumor viewed from behind, the lungs on either side.

Restrictions by the parents prevented examination of the cerebrum.

Microscopic Examination.—The spleen shows congestion of its pulp, with increase in the pulp cells; the malpighian corpuscles are well formed; the trabeculae are normal. There are many eosinophil leukocytes in the sinuses, both of the myelocytic and polymorphonuclear type. The liver shows passive congestion, with slight fatty infiltration, not in excess of physiologic limits. The metastatic (?) nodules are either completely necrotic or calcified and give little or no clue as to their original composition. The large caseous mesenteric lymph node shows typical tuberculosis, with a zone of miliary tubercles surrounding a caseous center.

Examination of Tumor.—Macroscopic: The tumor in the mediastinum is roughly conical in shape, its base measures 8 cm. laterally and 11 cm. anteroposteriorly, while its axis is 11 cm. in height. It is homogeneous, for the greater part, pearly yellowish white and occupies the entire mediastinum, surrounding all the large vessels, the bronchi, trachea and the peribronchial lymph nodes. It is lobulated, the lobules being of a type to suggest local overgrowth of a single organ, rather than aggregations of enlarged nodes. Cross sections made at various levels (clearly seen in the posterior view in the illustration, Fig. 3) show that it has included everything as high as the thyroid gland; it is as though moulten wax had been poured into the anterior mediastinum and had flowed out laterally and posteriorly before hardening; in the thorax the esophagus alone has escaped inclusion. The tumor resembles cornstarch blanc mange in its yellowish white color, but is of an extremely dense and almost cartilaginous consistence. The trachea is compressed anteroposteriorly, until it is a mere slit, a millimeter or so in this diameter (Fig. 4). This compression is present practically throughout its entire length. Here and there lymph nodes are embedded in the tumor mass, but they are totally different in appearance, being of a soft consistence and more yellow tinge. The tumor shows areas of necrosis at intervals throughout its substance, but they are few and widely separated from one another. They are of irregular outline, somewhat softer in consistence than the tumor and of a canary yellow color. The growth has metastasized by way of the lymphatics into the pleura and pericardium in its immediate vicinity, where it forms several plaques as already described. It will readily be seen that the tumor, then, occupies the site of the thymus and has encroached directly on the pericardium, heart, pleura and lungs.

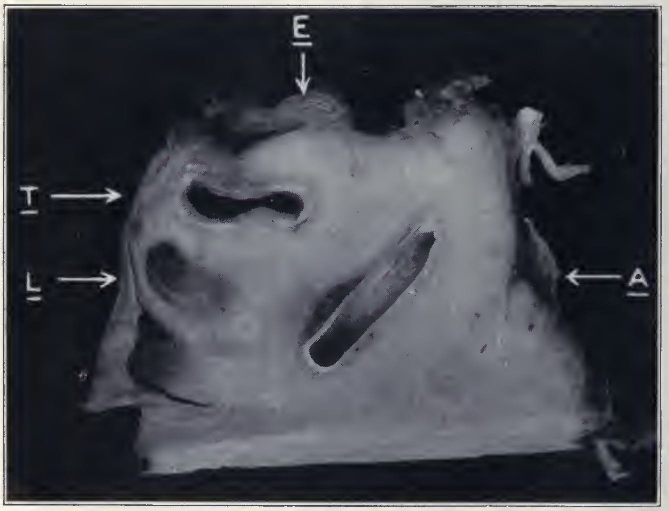

Fig. 4.—Transverse section of tumor at level of arch of the aorta. E = esophagus; T = trachea; L = an included lymphnode. An arrow, "A," points to the diagonally situated arch of the aorta.

Microscopic: The tumor is made up of innumerable lymphocytoid cells which, at first glance, might be taken for microlymphocytes. Closer examination, in sections stained with Mallory's eosin-methylene blue, shows that they differ from these in several respects: They are somewhat larger, more polygonal in outline, have an acidophile rather than a basophile cytoplasm and their nuclei are vesicular, contain a nucleolus and are poor in chromatin when compared with those of the microlymphocytes (Fig. 5). They lie, furthermore, in a dense feltwork of collagen fibrils and fibers, which in some cases form basket-like nests, or alveolar spaces in which the tumor cells lie more or less crowded together (Fig. 6). Often, too, one can demonstrate delicate anastomosing filaments, or processes from the cytoplasm of these cells, which connect them either with one another, or with the fibrous reticulum in their neighborhood. They do not give the oxydase reaction, when stained by Goodpasture's[2] method. Their

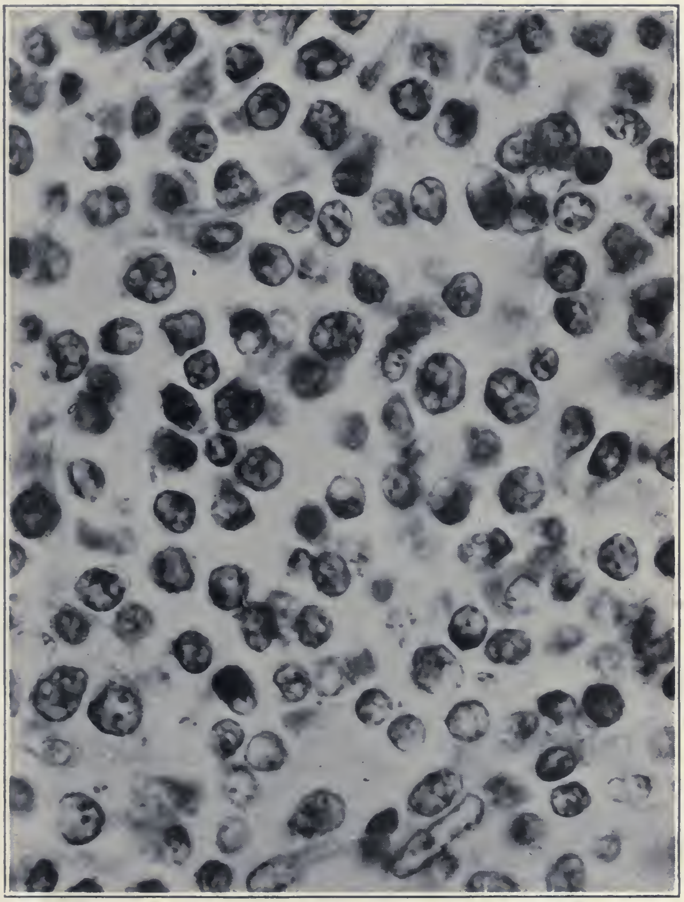

Fig. 5.—Oil-immersion photomicrograph of nonfibrous portion of the tumor. Slightly more than 1,000 diameters magnification. Phosphotungstic acid-hematoxylin.

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[2] Goodpasture, E. W.: J. Lab. & Clin Med. **4**:442, 1919.

size is fairly constant in certain localities (Fig. 5), some parts of the tumor showing larger cells than do others, but the cells of each part are usually of about the same size. They average from 4.5 to 6.0 microns, occasionally attaining a long diameter of 7.5 microns. Mitoses are very thickly distributed and usually occur in the smaller type of cells. There are a good many eosinophil leukocytes present, both types being scattered throughout the tumor and usually being more or less locally grouped. Some rather larger cells are found containing one or two large masses of eosinophil material, probably phagocytosed erythrocytes. Besides the tumor cells, there is a larger type of cell of a vesicular character; with large, pale nucleus (from 10 to 14 microns) and a well marked nucleolus. Their cytoplasm may be vacuolated; when it is thinned out and stained with phophotungstic acid hematoxylin one finds blue fibrils in its substance. These cells closely resemble swollen fibroblasts, though they may represent thymic reticulum cells. They are often piled up locally in the vicinity of blood vessels, where they might be mistaken for young Hassal's corpuscles. As vessels can usually be demonstrated as being intimately connected with their appearance, it seems more likely that they are endothelial phagocytes, or fibroblasts. There are a few giant cells at the margin of the necrotic areas in one of the ten or more blocks cut from the tumor; they are somewhat like those seen in a Hodgkin's granuloma, with large, vesicular nuclei which are

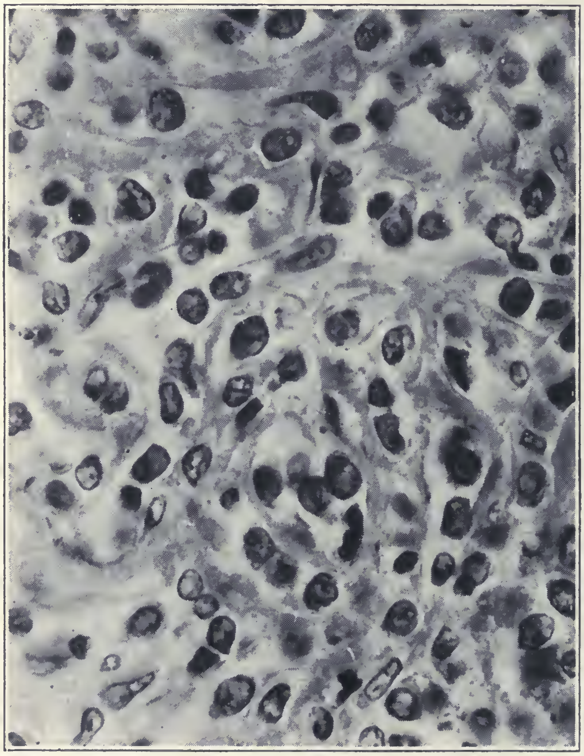

Fig. 6.—Showing the fibrous reticulum of the tumor; oil-immersion photomicrograph, 1,000 diameters. Phosphotungstic acid-hematoxylin.

more or less lobulated. Sometimes they are multinuclear, but they never have as dense a cytoplasm as the so-called "foreign body giant cells." They are found only in the situation mentioned.

The stroma, or reticular network of collagen fibrils, stains bright red with acid fuchsin and deep red with phosphotungstic acid hematoxylin. It varies much in density, being in the form of a delicate reticular network here and a dense fibrous matrix in another situation. The two types are shown in Figures 5 and 6. It is this feltwork that gives the tumor its deceptively cartilaginoid consistence.

Lymph nodes taken from near the tumor show hyperplasia, many eosinophils and a considerable number of small cells which are indistinguishable from the tumor cells and lie among typical lymphocytes, with which they contrast rather sharply. There are no giant cells in these nodes, and their reticulum appears to be normal and not fibrosed. There are one or two nodes, however, which show a very remarkable hyperplasia and proliferation of their endothelial elements, particularly those of the lymph sinuses between nodules. These are often massed into thick bands or cords, the vascular endothelium in this situation seemingly sharing in the process, although to a lesser degree. In those places where the tumor has penetrated the myocardium, this is a direct infiltration from the epicardial fatty tissue near the anterior interventricular sulcus and near the apex, to a depth of 270 microns. The structure of the growth does not differ microscopically here from that seen elsewhere.

SUMMARY OF FINDINGS

We have a very hard, lobulated mediastinal tumor, occupying chiefly the anterior mediastinum; lying just behind the sternum, but not infiltrating the bone. It shows metastasis by direct lymphatic extension, with three possible minor metastases at a distance. It does not penetrate the lung nor other neighboring organs much more deeply than their serous coverings or sacs. It is composed chiefly of small cells, resembling microlymphocytes, but having vesicular nuclei, acidophil cytoplasm and tending very slightly to anastomose with one another by means of slender processes. This applies only to a decided minority of their number, the majority being unconnected with each other, or discrete. The rest of the tumor is chiefly collaginous connective tissue. Neighboring lymph nodes, while they show a few discrete tumor cells in their sinuses, are usually respected by the tumor and not incorporated in its mass.

REVIEW OF LITERATURE

The literature on this subject is characterized by its comparative scantiness and by the wide divergence of opinion shown by the various writers as to the true status of these tumors. Such textbooks as Borst's,[3] Lewin's,[4] Ribbert's[5] and Wollf's[6] pay but passing attention to them. Schridde,[7] in Aschoff's "Pathologische Anatomie," gives a good description of tumors of thymic origin, which is fairly comprehensive considering its brevity. Since 1911, very little has been written on the subject. Of the more recent articles, one by Ewing,[8] and another by Vanzetti,[9] present extremely good reviews of the various theories that have been advanced as to the origin and character of thymic tumors, and the authors report several cases and give full bibliographies on the topic. Rubaschow's [10] case report and article is very helpful, while Wiesel's [11] much longer paper on the pathology of the thymus, which stresses the clinical features of these tumors, is valuable but rather rambling and prolix. Rubaschow has compiled a list of the tumors of the thymus described up to 1911, combining one of Hoffmann's which brought them up to 1896. It totals about seventy-five cases, of which fifty-two were described as "sarcomata" of various sorts, twelve as carcinomas and the rest variously. He gives the names of the writers concerned and the dates of publication. Since 1911 one can find but few reports, less than a dozen.[12]

---

[3] Borst, M.: Die Lehre von den Geschwülsten, Wiesbaden, 1902.

[4] Lewin, C.: Die bösartigen Geschwülste, Leipzig, 1909.

[5] Ribbert, H.: Geschwulstlehre f. Aertze u. Studierende, Bonn, 1904.

[6] Wollf, J.: Lehre von der Krebskrankheit, Jena, 1911.

[7] Schridde, H.: Aschoff's "Pathologische Anatomie," Jena, 1911, 177; Münch. med. Wchnschr. **58**:2593, 1911.

Rubaschow reports a case more closely corresponding to the one described in this paper than any that could be found, although it occurred in a man, aged 62. The "type cells" were very small lymphocytoid affairs, and there were aggregations of larger cells, such as I have already described. Two of Ewing's cases come very close to ours in appearance. It is possible, in reviewing the literature, to find descriptions of tumors in which the type cells vary all the way from small, disconnected lymphocytoid cells, through larger, more or less anastomosing cells, to a definitely epithelial type of large cell, which may finally attain a degree of differentiation resembling that of the epidermoid carcinoma, on the one hand, and an adenoma or adenocarcinoma, on the other. Our case stands at the lowest point in the scale; Rubaschow's and Chiari's [13] may be slightly more advanced. Two of Ewing's come next, with larger, more polygonal cells, which have a tendency to anastomose, or to be connected with the reticulum by delicate processes (just as was found in the upper portions of our tumor). Vanzetti's [9] is still further differentiated, the cells in his tumor being frankly epithelial in appearance; and then come numerous examples of true carcinoma.

The presence of much connective tissue and many eosinophils have led several authors to compare this tumor with Hodgkin's granuloma, and to suspect an infectious origin. Those of us who consider the latter disease a form of neoplasm can dismiss this contention by attributing the presence of increased connective tissue and the eosinophils to a sympathetic overgrowth or irritation of elements already present in the parent organ. Giant cells, of whatever type found, obviously present no stumbling block.

---

[8] Ewing, J.: Surg., Gynec. & Obst. **22**:401, 1916.

[9] Vanzetti, F.: Arch, per le sc. med., Torino **40**:264, 1916.

[10] Rubaschow, S.: Virchow's Arch. f. path. Anat. **206**:141, 1911.

[11] Wiesel, J.: Ergebn. d. allg. Path. u. path Anat. **15**:416, 1912

[12] Barbano, C.: Pensiero Med. **2**:701, 1912. Roccavilla, A.: Gazz. d. osp. **34**:903, 1913; Riforma med. **21**:337, 1915. Simmonds, M.: Ztschr. f. Krebsforsch. **12**:280, 1912. Speed, K.: Surg. Clin. **1**:643, 1917. Perrero, E.: Riv. di. clin. pediat. **9**:241, 1913.

[13] Chiari, O. M.: Zentralbl. f. Path. **22**:8, 1911.

HISTOLOGY OF THYMUS

Before going any further into this discussion, it would be well to consider the general aspects of the thymus in its relation to tumors of the mediastinum. It will be seen that so long as there is uncertainty as to the histology of this organ, just so long will there be doubt and disputes as to the histogenesis of tumors arising therefrom. Of the various histologic elements of the organ, three are the subject of speculation and dispute. The small thymic cell of the cortex ranks first as a bone of contention; is it a lymphocyte, or is it a modified form of epithelial cell? Dantchakoff,[14] Hammar [15] and Maximow take the former view; while Bell, Prenant, Schridde, and more recently Pappenheimer [16] claim its descent from the epithelium.[17] A clearer understanding of the difficulties surrounding this question will be gained by reading Hammar's "Fuenfzig Jahre Thymusforschung," [15] or Pappenheimer's splendid exposition.[16]

The occurrence of eosinophil cells in the thymus is another cause for discussion. Are they eosinophil leukocytes derived from the circulating blood, or are they cells peculiar to this organ? Hassal's corpuscles, although admittedly epithelial in character, represent another unknown quantity, insofar as their physiologic function is concerned.

THYMUS ORIGIN OF TUMOR

When we come to consider tumors derived from these elements, we naturally enough encounter the same questions, the same dissensions, the same difficulties. Are they epithelial and hence carcinomas, or should they be called sarcomas and lymphosarcomas? Not only do we have to deal with such problems, but the question arises as to which mediastinal tumors may be considered thymic in origin and which derived from the lymph nodes of this region.

It seems to be more or less agreed that the following facts point to the thymic origin of a tumor:

1. The situation of a large, not too lobulated, firm tumor at the site of the thymus, in the anterior mediastinum.

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[14] Dantchakoff, V.: J. Exper. Med. **24**:87, 1916.

[15] Hammar, J. A.: Anat. Hefte **19**:1-274, 1909; 43, 201, 1911.

[16] Pappenheimer, A.: J. Med. Res. **17**:1, 1910.

[17] From a personal conversation with Dr. Pappenheimer, a few weeks ago, I surmise that he has changed his opinion and joined the "lymphocytic camp."

2. Extension downward behind the sternum, without infiltrating the bone.

3. Involvement of the pericardium and pleura by direct lymphatic extension.

4. A resemblance to thymic tissue on histological examination. The finding of Hassal's corpuscles is helpful, but not essential.

Ewing, Schridde, Rubaschow and Letulle[18] are fairly well in accord on these points, some being more specific in their statements than others. Virchow (quoted by Wiesel[11]) maintained that the thymic tumors involved the pericardium first, while the lymphosarcomas attack the lungs or pleura. Hoffman (quoted by Vanzetti[9] and Wiesel[11]) denied that one could make any decision in the matter, the two types of tumor being absolutely indistinguishable one from the other. He appears to be alone in his opinion, nobody seeming to accept so sweeping a view. He also denies that the presence of Hassal's corpuscles proves anything at all. Letulle[18] states that the parenchyma of the lung can only be invaded secondarily by thymic tumors, thus paraphrasing Virchow's statement. He imposes other conditions, such as eccentric pressure on neighboring viscera, but they seem less essential. Vanzetti feels that the small-celled type of thymic tumor so closely resembles a true lymphosarcoma, that one must be extremely careful in diagnosing one from the other; a fact that no one will dispute.

Another point on which most authorities agree is that the tumors are apt to be of the small-celled or sarcomatoid type in youth; while they are large-celled epithelial, or sarcomatous, in later years, after fifty. In this connection it is interesting to note that Rubaschow's case occurred in a man, aged 62, and yet was of a definitely small-celled type, which he considered epithelial.

When one compares the thymoma with a true lymphosarcoma, one finds many similarities; but this is, perhaps, to be expected in view of the similarity of the small thymic cell and the lymphocyte. The following points seem to be against the lymphocytoid type of thymoma being a true lymphosarcoma.

1. The type cell is almost identical with the small thymic cell.
    - (a) The nucleus is large, more or less ovoid and may contain a well marked nucleolus.
    - (b) The cytoplasm is often acidophil, never strongly basophil like that of the microlymphocyte, and may be present in sufficient quantities to give the cell a polygonal outline. Anastomosing processes may be present.

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[18] Letulle: Arch. Gen. de med. **2**:641, 1890.

2. Lymphnodes taken from near the tumor, although they may show isolated tumor cells in their sinuuses under the microscope, are not definitely incorporated in the tumor mass. They stand out clearly demarcated, even when surrounded on all sides by the tumor, both when viewed in the gross, or with the microscope. Rubaschow has stressed this point. They seem to hold themselves aloof from the tumor process, not only locally, but also in more distant parts of the body. Metastases, when they occur at a distance from the tumor, generally do so in the spleen or liver instead of in lymphnodes, as one would expect, were this a true lymphosarcoma. The mesenteric nodes in our cases are enlarged, but show either tuberculosis or simple hyperplasia, no tumor metastases being found.

3. Lymphoblasts and collections thereof are not found in the tumor to any appreciable extent, mitoses occurring in the smaller cells, or in larger cells totally dissimilar from the large lymphocyte.

4. There is a variable tendency to form alveoli, or nests of small cells, although lumina are not definite enough to warrant speaking of glandular structure.

SUMMARY

The information to be gleaned from a review of this subject, as well as from what little I can add to it, seems to point rather strongly to an epithelial origin of the tumor in question. One starts with a cell which is almost, but not quite identical in appearance with the microlymphocyte, but once it begins to differentiate the similarity is rapidly lost. It would seem to be wisest not to put too much stress on an argument based on a series of transitional stages pieced together from groups of cases occurring in individuals of different ages and reported by an equally variable number of observers with opposed points-of-view. Such a series is, nevertheless, very suggestive and not unsupported by supplementary evidence from the embryologic standpoint. On the one hand, as Ewing has said, are the small-celled, sarcomatoid tumors; on the other the carcinomatous; while between these are all the intergradations, which to him suggest an infectious process when they appear in the same tumor. There is very little reason to regard such a tumor as ours as being of infectious origin, while there is a great deal to point towards its being a true neoplasm. Although the presence of eosinophils and a few large cells are reminiscent of Hodgkin's granuloma, these could be explained by the irritation of the neoplasm on its host, so that it seems best not to consider the two conditions as being at all related to each other.

CONCLUSION

In conclusion, there seems to be little doubt that these small-celled thymic tumors fulfill the conditions we have already reviewed and are, whether lymphosarcomas or not, still of thymic origin and different from the lymphosarcomas that originate in lymphnodes. The decision of their true status rests with the histologist, who must first determine without a doubt, the origin of the small thymic cell. Once this has been done, the question will be settled automatically, so far as the pathologist is concerned.

I am much indebted to Prof. Lewis Bremer, of the Department of Anatomy of the Harvard Medical School, for the use of his photomicrographic apparatus, and to his staff for their aid and advice as to its use. Dr. Percy Brown has kindly supplied me with the Roentgenograph which is reproduced in this article.

PRECIPITINS FOR EGG ALBUMIN IN STOOLS*

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The preparation of the stools was the same in these cases as that reported in a previous article.[1]

Anti-egg white rabbit serum of a titer of 40,000 was used. Titer equals highest dilution of egg white in salt solution in which the serum produced precipitate by contact method after one hour at room temperature.

The first group (Table 1) consisting of 103 stools from 24 cases showed three positive reactions. These stools were all from children two years or over. Two of the positive reactions occurred in the case of idiocy (Case 6). This child had a large quantity of egg in the diet since it was about the only food which she would take readily. To the other children egg was usually given in the form of ice cream and pudding only on Sunday afternoons, but occasionally during the week. The single other positive reaction that occurred in the stool of Case 4 occurred within forty-eight hours after taking this diet; but of seventeen other stools with the same relation to the diet, no positives were found.

After this initial group, it was decided to study a few cases with egg albumin given to the amount of a teaspoonful each day. For this three different types of cases were chosen. Case 1, a control case, was fed through a gastrostomy wound; the second case, a case of intestinal infantalism, and a third one of general eczema. In seventeen stools obtained from these children only one showed a doubtful reaction (Table 2).

In the third group of thirty-three cases of infants 2 years old or under, there were 221 stools. In only two of these cases was the age over 1 year. Many of them were newborn infants who had received a dilute albumin water to the amount of 10 c.c. of egg albumin to 500 c.c. of water, which was given to these infants in place of the usual boiled water. From this group 221 stools were examined with five positive reactions. One of these reactions occurred in a new-born infant who had been given the egg albuumin mentioned above. In the other three children who gave positive reactions, we know of no way to account for these, since in no instance was egg albumin present in the diet.

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* From the McCormick Memorial Institute and Children's Ward of the Presbyterian Hospital.

* Read before American Pediatric Society, May 30-June 1, 1920.

1. Hektoen, L., and Grulee, C. G.: Am. J. Dis. Child. **18**:1 (July) 1919.

TABLE 1.—EXAMINATION OF STOOLS OF OLDER CHILDREN FOR EGG ALBUMIN

No.	Diagnosis	Age, Years	No. of Stools	Positive Reaction
1.	Chorea; myocarditis; Ludwig's angina; tonsillitis.....	8	28	0
2	Epilepsy..	10	9	0
3	Syndactylism..	5	2	0
4	Appendicitis..	8	9	1
5	Chronic osteomyelitis (fibula).........................	9	9	0
6	Idiocy..	3	14	2
7	Fractured arm...	6½	2	0
8	Otitis media; mastoiditis..............................	4	2	0
9	Osteomyelitis os calcis................................	8	5	0
10	Abscess of cervical glands.............................	6	2	0
11	Diabetes mellitus.......................................	2½	1	0
12	Chorea..	8	5	0
13	Skull fracture..	4	1	0
14	Congenital glaucoma....................................	2½	1	0
15	Chronic ileocolitis.....................................	2	2	0
16	Eye injury...	5	2	0
17	Chorea..	8	2	0
18	Otitis media...	2	1	0
19	Cholecystitis..	12	1	0
20	Tenoplasty for old poliomyelitis......................	10	1	0
21	Tuberculous meningitis.................................	3	1	0
22	Rectal polyp...	4	1	0
23	Encephalitis lethargica.................................	2½	1	0
24	Chronic tonsillitis.....................................	7½	1	0
	Total...	..	103	3

TABLE 2.—TEST CASES GIVEN ONE TEASPOONFUL OF EGG ALBUMIN PER DAY

No.	Diagnosis	Age, Months	No. of Stools	Positive Reaction
1	Stricture of esophagus..................................	13	2	0
2	Intestinal infantalism..................................	22	6	0
3	Eczema..	19	9	1 (?)
	Total...	..	17	1 (?)

TABLE 3.—RESULTS OF EXAMINATION OF STOOLS OF INFANTS

No.	Diagnosis	Age	No. of Stools	Positive Reaction
1	Prematurity...........................	Newborn	10	0
2	Prematurity...........................	Newborn	4	0
3	Prematurity...........................	Newborn	1	0
4	Normal..................................	Newborn	3	0
5	Intracranial hemorrhage...............	Newborn	1	0
6	Normal..................................	Newborn	6	0
7	Normal..................................	Newborn	3	1
8	Normal..................................	Newborn	5	0
9	Normal..................................	Newborn	3	0
10	Normal..................................	Newborn	4	0
11	Normal..................................	Newborn	2	0
12	Normal..................................	Newborn	2	0
13	Normal..................................	Newborn	4	0
14	Normal..................................	Newborn	2	0
15	Normal..................................	Newborn	1	0
16	Normal..................................	Newborn	2	0
17	Hydrocephalus meningocele; prematurity................................	1 mo.	16	0
18	Prematurity...........................	5 wks.	9	0
19	Hare lip; cleft palate..................	2 mos.	10	0
20	Pylorospasm............................	2 mos.	7	0
21	Infantile eczema.......................	11 wks.	16	0
22	Infantile eczema.......................	3 mos.	14	2
23	Pylorospasm............................	3 mos.	7	0
24	Decomposition.........................	3 mos.	1	0
25	Pylorospasm............................	14 wks.	20	0
26	Rumination.............................	5 mos.	14	1
27	Congenital syphilitic hydrocephalus....	6 mos.	8	0
28	Hydrocephalus.........................	6 mos.	9	1
29	Weight disturbance....................	7½ mos.	23	0
30	Rickets.................................	1 year	5	0
31	Meningeal hemorrhage..................	1 year	5	0
32	Infantile eczema.......................	21 mos.	2	0
33	Cervical cellulitis; pyelocystitis.........	2 years	2	0
	Total..................................	....	221	5

It would seem from these results that egg albumin is in nearly every instance completely broken down by the digestive processes in infants and children. This holds good not only for children and older infants, but also where the egg albumin is used in small quantities for the new-born as well. There is only one other possibility, and that is that the egg albumin instead of being broken down in the process of digestion is absorbed unchanged. We do not feel that specificity of the precipitin reaction for egg albumin is to any degree disproven by the fact that it was found to be positive in stools where no egg had been present in the diet. We would be inclined to attribute such reaction to the complexity of the stool.

I wish to take this opportunity to thank Dr. Ludvig Hektoen, who has been kind enough to have the precipitins prepared and the experiments done under his personal supervision; and to Dr. B. E. Bonar for the preparation of the fecal extracts.

THE HEMORRHAGIC TENDENCY AS A FREQUENT CAUSE OF CRANIAL HEMORRHAGE OF THE NEW-BORN *

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At the meeting of the Section on Diseases of Children of the American Medical Association in Chicago, June, 1918, I expressed the belief that an important factor in intracranial hemorrhage occurring during, or soon after birth, was the so-called hemorrhagic tendency of the new-born, frequently expressed in hemorrhages from the mucous surfaces in various portions of the body.[1] A case in point was cited of an infant, 3 days old, in which, following diagnosis, a cranial decompression was performed, revealing a general hemorrhagic oozing of the pia. Convulsions and other cranial pressure symptoms were relieved, but vomiting of blood, and hemorrhage from the rectum, caused death a day later, in spite of prompt blood transfusion from the father. The free use of lumbar puncture and of human blood serum, horse serum or thromboplastin was suggested at that time in every instance where intracranial hemorrhage of the new-born is suspected. I said in part:

> . . . I am firmly convinced that all of the causes are not maternal. Probably many cases occur after rapid delivery in which the cause lies not with the mother but with the child. I am sure many of us have seen hemorrhage of the new-born in connection with intracranial hemorrhage in infants. I think we would see many more if the children lived long enough. I think many of the cases which do not show rupture in the meningeal artery are not frank hemorrhages so much as oozing of the vessels of the pia, perhaps not producing the classical symptoms so early as hemorrhage from the meningeal artery. For that reason we can say that there is a hemorrhagic tendency, some degrees of permeability of the vessels, not going on to the extent that will produce characteristic vomiting of blood, but increased fragility of the vessels of the infant, which does produce, even after rapid labor, symptoms of hemorrhage of the brain. There is no doubt that great relief can be obtained by lowering intracranial pressure through lumbar puncture. As has been stated by the essayist, it is of great value as a diagnostic measure, and should never be omitted in any case of intracranial hemorrhage in an infant. It certainly can do no harm to use some method to increase the coagulability of the blood—blood serum, citrated blood or something of that sort, in attempting to offset the tendency to hemorrhage that undoubtedly exists in many of these children.

At the Providence Hospital, Washington, D. C., within the last fifteen months, this procedure has been followed in seven cases. In all new-born infants showing within twelve to twenty-four hours after

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* From the Pediatric Department of Georgetown University and the Obstetrical Wards of Providence Hospital.

[1] Brady, Jules: Discussion by Foote, J. A. M. A. **71**:347 (Aug. 3) 1918.

birth respiratory distress and blueness, with or without muscular rigidity and twitching, lumbar puncture was performed. In every instance where these symptoms were observed within twenty-four hours after birth, the lumbar puncture showed amounts of blood, varying from a deep to a light claret color, and occasionally small clots. Both horse serum and thromboplastin were used hypodermically. Ten c.c. was the amount injected, the horse serum being employed, however, in five of the seven cases. One of these infants died; the others recovered uneventfully. In only one was lumbar puncture repeated. Six of these which we have been able to trace seem normal in every way so far, although the ultimate results cannot be predicted definitely at this early date.

Corroborative of these clinical observations is the report by Dr. Margaret Warwick of thirty-six necropsies at the University of Minnesota, on still-born infants or those dying within a short period after birth.[2] Fifty per cent. of these showed hemorrhages in the dura, over the brain surface or in the ventricles. Only one of these was a forceps case. Two out of eighteen were born dead. In eight, or 50 per cent., of those showing cranial hemorrhage, hemorrhages were found in other organs. Five of these infants vomited blood before death, and all showed increased coagulation time. Warwick mentions the frequency of punctate hemorrhages seen in the pleura and peritoneum in routine necropsies of the new-born. A number of reports of hemorrhage in the fetus or in various organs of the new-born infant are on record. Paul[3] found retinal hemorrhage of the infant in 50 per cent. of premature labors, 40 per cent. of prolonged labors, and 20 per cent. of normal labors.

Osler once reported finding a cranial hemorrhage in the brain of a fetus, the mother of which had died from typhoid fever. Kundrat[4] believes that many cranial hemorrhages in the new-born occur without any visible symptoms, the small amount of exuded blood absorbing rapidly. Moreover, cases are frequently mistaken for atelectasis, and this same writer found that practically all cases show partial atelectasis of one or both lungs. This is well borne out by the clinical symptoms of blueness and difficult breathing, which frequently dominate the clinical picture.

It is interesting, in view of these observations, to report still another infant with cranial hemorrhage and frank hemorrhages from the mucous surfaces which responded to early treatment in a surprising manner.

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2. Warwick, Margaret: Am. J. M. Sc. **158**:295, 1919.
3. Paul: Inaug. Dissert., Halle, 1910.
4. Cited by Warwick, loc. cit.

REPORT OF CASE

Case (8076).—Baby, delivered after a long labor, midforceps operation by Dr. Davenport White. Breathed normally and cried. No traumatic marks on head. Weight, 8 pounds 4 ounces. Twelve hours after birth became blue, and respiration was labored. Some tonic twitching of left arm and hand. A monotonous cry. Coagulation time of blood exceeded nine minutes. Was given 10 c.c. horse serum. Lumbar puncture was made, 10 c.c. of fluid was withdrawn, red in color with numerous small soft clots. Red blood cells abundant microscopically. Fifteen hours after delivery infant vomited red blood mixed with mucus. Hemorrhages occurred within a few hours from the rectum, nose, stomach and ear. Ten c.c. of thromboplastin was given under the skin on the appearance of blood in the vomitus. No further hemorrhages occurred, the infant began to suck vigorously, and except for a febrile course for a few days, had no further symptoms. At the age of 9 weeks infant shows an average gain of 2 ounces a week on artificial food, but tolerates increased feeding rather poorly.

The surgical treatment of this condition is one which yields brilliant results when pressure symptoms allow a focal diagnosis. The work of Cushing [5] and of Sharpe [6] emphasizes that simple surgical relief of pressure often suffices to avert the horrible after paralysis known as Little's disease, and that this treatment has its distinct indications. Sharpe's splendid essay is rich in valuable information concerning the surgical aspects of this condition, and the indications which in certain circumstances make a resort to surgery an inevitable proceeding. However, early recognition of the condition and treatment directed toward increasing blood coagulability will be beneficial in that large number of cases where the hemorrhage comes from very small vessels, even as a preliminary toward surgical decompression, when that is found necessary.

It is true that hemorrhage may occur in the infant's skull, produce all the classical symptoms and yet be followed by apparent recovery without any special treatment directed toward blood coagulability or the relief of pressure. Two such cases have come under my personal observation. One of the patients is now 6 years old, the other 4 years. Neither of these children shows any muscular abnormality today. This is corroborative of Kundrat's [4] observation, and of the necropsy work of Wehe [7] who found that 12 per cent. of 959 infants at necropsy showed evidence of having had cranial hemorrhage. It also speaks for an unusual capacity of the infant organism in absorbing coagulated blood, which may be taken advantage of in treatment along the lines I have suggested.[8]

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[5] Cushing, Harvey: Am. J. M. Sc. **130**:563, 1905.

[6] Sharpe, W.: Internat. Clin. **4**:258, Series 29.

[7] Wehe, A.: Inaug. Dissert., Kiel, 1889.

[8] Seitz: Zentralbl. f. Gynäk. **36**:1, 1912.

CONCLUSIONS

1. The tendency toward hemorrhage in the new-born is frequently first manifested as intracranial hemorrhage, and it is important to recognize that this may be and often is a local manifestation of a general condition.

2. The early use of lumbar puncture and the hypodermic administration of substances that tend to increase blood coagulability are rationally indicated in every case of suspected intracranial hemorrhage of the new-born, even prior to operation.

3. The suggestion that blood coagulation tests be performed as a routine on the new-born infant is one that merits consideration.

ACTIVE IMMUNIZATION AGAINST DIPHTHERIA IN A LARGE CHILD-CARING INSTITUTION

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During the past few years our ability to detect antitoxin immunity in diphtheria has been greatly simplified by the introduction of the Schick test. Since this test has been shown to be a very accurate measure of the body's antitoxic immunity, we are now able by its use to measure the value of any new form of prophylactic treatment which depends on the production of antitoxin. A new form of preventive treatment is the toxin-antitoxin injection first advocated by Theobald Smith and William H. Park, and first actually employed in human beings by von Behring. During the past five years we have been able to use this active immunization and to control it by means of the Schick test in the Home for Hebrew Infants. This institution is especially adapted for this work, as the same children can be observed and retested for a period of about five years; furthermore, the ages of the children coincide with the most frequent age incidence of diphtheria.

During the year 1915, diphtheria had been endemic in the institution, and there were six deaths due to the disease. It was a problem, therefore, to attempt to reduce if possible the morbidity and consequent mortality. We welcomed the opportunity to separate, by means of the Schick tests, those immune from those susceptible, and to attempt to increase the number of the former by means of toxin-antitoxin injections. The diphtheria toxin used in the Schick test was obtained in bulk from the Research Laboratory of the New York City Department of Health. Dilutions for the test were made from the pure diphtheria toxin as follows: One hundred times the minimum lethal dose for the guinea-pig was diluted up to 10 c.c. with physiologic sodium chlorid solution. This primary dilution does not deteriorate appreciably for a period of two weeks if kept cold in the icebox. The final dilution, good for twenty-four hours only, is made by taking 1 c.c. of the primary dilution, and adding 99 c.c. of physiologic sodium chlorid solution. The amount injected intracutaneously for the Schick test is 0.2 c.c. of the final dilution representing $\frac{1}{50}$ minimum lethal dose for the guinea-pig. The injection is best made on the anterior surface of the forearm in its upper third, using a 1 c.c. Record syringe, with a fine platinum iridium needle. Schick injects $\frac{1}{50}$ minimum lethal dose for the guinea-pig in only 0.1 c.c. of physiologic sodium chlorid solution. The use of 0.2 c.c. of the final dilution is preferable because the area of the reaction is greater in extent and the chance of error in the amount injected is less. In borderline cases the Schick method gives the stronger reaction.

A negative Schick test denotes that there is sufficient antitoxin in the tissues to neutralize the diphtheria toxin injected, and, therefore, enough to protect the individual. A strongly positive Schick test denotes that there is no antitoxin in the tissues and, therefore, the individual is not protected by antitoxin. Bactericidal substances may, however, be present. Therefore, the person is probably, but not certainly, susceptible. A moderately positive reaction indicates a faint trace of antitoxin. The positive reaction appears usually in from twelve to twenty-four hours, but may be delayed another twenty-four or forty-eight hours. It is characterized by a circumscribed area of redness and slight infiltration at the site of the injection, measuring from 1 to 2 cm. in diameter. This persists usually for at least seven or ten days and then fades with superficial scaling and a dark brown pigmentation. I have seen the pigmentation persist for as long as three or four months. The positive reaction is dependent on the local destructive action of diphtheria toxin on the tissue cells in the absence of antitoxin. The moderately and faintly positive reactions which occur in those having faint traces of antitoxin are characterized by lesser degrees of redness and infiltration than the strongly positive. The pseudoreaction, a pure sensitization phenomenon occurring in older children and adults, was rarely seen in the young children tested.

For convenience, the strongly positive reaction can be designated as +, the moderately and slightly positive as ± and the very faintly positive as $\underline{\pm}$. Children giving ± and $\underline{\pm}$ reactions have been included in the tables with the positive cases. In this institution, for the sake of greater safety they were in all cases given actively immunizing toxin antitoxin injections.

The tables summarize the reactions obtained in children of various age groups from 1 month to 6 years. For comparison I have appended tables showing Shick's and Zingher's results.

As shown in Table 1, 37 per cent. of the children in all probability were susceptible to diphtheria. These susceptible children were most frequently encountered between the ages of 6 months and 4 years. They were fewest in number in infants younger than 6 months or older than 4 years. The infrequency of positive reactions during the first half year of life is owing probably to an immunity inherited from the mother. That this immunity may gradually be lost by the infant was well illustrated by retesting the infants from time to time. It was found that a number of those who gave negative reactions during the first two years of life became positive later on; in other words, their inherited passive antitoxic immunity was gradually lost. Of a total of 119 children under 1 year of age giving negative tests, nineteen, or 16 per cent., became positive from three to six months later. When first tested, ten of these were in their first half year of life, and nine were in the second half year. Thirteen of 108 negative children, or 12 per cent., became positive during the second year, and five of 125 negatives, or 4 per cent., became positive during the third year of life. Table 4 illustrates this loss of inherited immunity.

The tests in certain families made on members under 3 years of age are also of interest. Of seventy-two families tested, two or more members gave the same Schick test in fifty-five families. Variations occurred in seventeen families as follows: In thirteen instances the younger member gave the positive Schick test and the older the negative; in four instances the younger member (in each case under 1 year of age), gave the negative Schick test, while the older gave the positive. This last variation is undoubtedly due to the disappearance of a passively transmitted immunity. These variations in the negative Schick tests during the first years of life emphasize the importance of frequently retesting infants in institutions. The retests should be done at least every three months.

It is worthy of note that when diphtheria was epidemic at the institution in 1915, in not a single instance did a child with a negative Schick test contract the disease. This record was uninterrupted until January and February, 1920, when influenza was epidemic. At that time nonspecific croup, in contradistinction to diphtheritic croup, was a rather frequent complication of influenza. Diphtheria antitoxin was administered to the croupy children having a positive Schick test and all recovered, except one. This child died, possibly of a complicating laryngeal diphtheria since the throat culture was positive for diphtheria bacilli. A necropsy was not made. Diphtheria antitoxin was administered in two very severe cases of croup and bronchopneumonia with negative Schick tests. One of these patients was intubated and died of bronchopneumonia. Diphtheria bacilli were not obtained from the cultures. The other patient had ulcerative stomatitis with extension of membrane to the pharynx and larynx and bronchopneumonia. A bronchoscopy was done for diagnostic purposes, and intubation was necessary shortly thereafter. Death followed in a few hours. Repeated throat cultures had been negative for diphtheria bacilli, cultures taken directly from the larynx and from a bit of tracheal exudate were positive. The facts that the child had given a negative Schick test and that a large dose of antitoxin had no effect, lead us to believe that the bacilli found in the trachea were not inciting the disease.

TABLE 1.—Results from Immunization Against Diphtheria at Home for Hebrew Infants

Age	Total	Negative Schick	Positive Schick	Percentage of Positive Schick Tests
1 to 6 months	97	76	21	21.6
6 months to 1 year	115	43	72	62.6
1 to 2 years	221	108	113	51.1
2 to 4 years	409	258	151	36.9
4 to 6 years	234	185	49	20.9
Total	1,076	670	406	37.7

TABLE 2.—Zingher's Results at Immunization

Age	Total	Negative Schick	Positive Schick	Percentage of Positive Schick Tests
1 to 6 months	101	82	19	18.8
6 months to 1 year	84	40	44	52.3
1 to 2 years	52	28	24	46.1
2 to 4 years	127	82	45	35.4
4 to 6 years	108	88	20	18.5
6 to 8 years	25	22	3	12.0
Total	497	342	155	31.1

TABLE 3.—Schick's Results at Immunization

Age	Total	Negative Schick	Positive Schick	Percentage of Positive Schick Tests
New-born	291	275	16	5.0
First year	42	24	18	43.0
2 to 5 years	150	55	95	63.0
5 to 15 years	264	133	131	50.0
Total	747	487	260	34.8

TABLE 4.—Results of Retesting Negative Schick Cases

Age	Negative Tested	Change to Positive Within Six Months	Percentage of Cases Changing to Positive
1 month to 1 year	119	19	16.0
1 to 2 years	108	13	12.0
2 to 3 years	125	5	4.0

TABLE 5.—Schick Retests on 252 Positive Children After Immunizing with Diphtheria Toxin-Antitoxin Mixtures

Time Interval after Injection	Number Tested	Results		Per Cent. Negative
		Positive	Negative	
Group 1. 3 to 4 months	252	68	184	73
Group 2. 9 to 10 months	130	12	118	91
Group 3. 22 months	50	0	50	100

Having ascertained that 37 per cent. of the inmates of our institution were susceptible to diphtheria, we proceeded to attempt to immunize these 252 children as follows: In the slightly or moderately positive, and the strongly positive cases three injections were made; in the faintly positive, two injections were made. The injections were given subcutaneously at intervals of one week, in the outer arm at the insertion of the deltoid muscle. Children under one year received 0.5 c.c., and those over 1 year 1 c.c. of the diphtheria toxin-antitoxin mixture at each injection. There was occasionally a little redness and swelling at the site of the injection and a rise in temperature in twenty-four hours up to 102 F., coming down to normal in another twenty-four hours. Vomiting occurred in one case and collapse in another with immediate recovery of the patient.

In order to test results, the children who had received the above treatment were subjected to the Schick test at two month intervals. Of these children, 252 in number, all of whom had been positive to varying degrees before injection, a large proportion were found to have become subsequently negative. The immunity developed in the children at different intervals; so that the later tests show a larger percent immune.

Of the 252 children originally tested, only 130 remained in the institution at the end of 9 or 10 months, and of this number only fifty remained at the end of twenty-two months.

From Table 5 it will be seen that very striking results were obtained. In from three to four months after toxin-antitoxin injections, 77 per cent. of the positive cases had become negative. In the group of fifty cases which were followed up as late as twenty-two months after injection, 100 per cent. had become immune. These marked results show the great practical importance of the active immunization of individuals susceptible to diphtheria, whether they are inmates of institutions or at large in the community. In this way an institution can be rendered practically immune. These results also emphasize the possible permanence of the immunity conferred, lasting perhaps during the life of the individual.

It is interesting to note that during a period of two years there was not a single case of diphtheria at the Home for Hebrew Infants. During this same period there were only about six positive diphtheria cultures in all throat and nose conditions. That this is mere coincidence is possible, but one may draw the conclusion that the toxin-antitoxin injections were probably instrumental in freeing the institution of diphtheria, despite the fact that for a time there were present a small number of susceptible children not immunized. It is also possible that the toxin-antitoxin injections rendered the nose and throat an unfavorable site for the growth of diphtheria bacilli. The blood being antitoxic the local toxin produced by the presence of the bacilli would not irritate the epithelial cells and thus the oral and nasal mucuous membrane would be rendered unfavorable for the growth of diphtheria bacilli.

CONCLUSIONS

1. Schick tests made on 1,076 children in an institution during a period of five years show that a negative Schick test is evidence of the presence of sufficient antitoxin in the tissues to protect the individual against diphtheria infection.

2. The moderate or slightly positive tests denote an insufficient amount of antitoxin in the tissues to protect the individual. The tests called very faintly positive show possibly sufficient antitoxin to protect; however, it is possible that the transfer of virulent organisms to these individuals may cause them not only to become carriers but to suffer from a superficial infection without any constitutional toxemia.

3. Tests made on seventy-two families showed that the younger members of the same family usually gave corresponding reactions to the Schick test. Where variations did occur, the younger member gave usually the positive and the older the negative reaction. Infants under 6 months, because of the transmitted immunity of the mother, were exceptions to this rule.

4. Changes in the Schick reaction from negative to positive during the first three years of life, due to the loss of an inherited immunity, were found to be sufficiently numerous to justify retesting during this period at intervals of a few months. This procedure is especially desirable in infant asylums.

5. The full duration of the active immunity conferred on individuals susceptible to diphtheria by the injection of toxin-antitoxin is not yet ascertained. In one series of cases the immunity persisted in 100 per cent. of a group of fifty children for at least twenty-two months. Workers in the Research Laboratory have found that the immunity once acquired lasts for at least four and one half years.

6. It is possible to render a child-caring institution diphtheria free. This has been accomplished for a period of five years at the Home for Hebrew Infants by injecting all susceptibles with toxin-antitoxin mixtures.

References

Schick, B.: Spezifische Therapie der Diphtherie, Centralbl. f. Bacteriol., 1 Abth., Jena, **57**:16-35, 1913. Ref. Beiheft, 16-35.

Schick, B.: Die Diphtheria Toxin Hautreaktion des Menschen als Vorprobe der Prophylaktischen Diphtherieheilseruminjektion, München. med. Wchnschr. **60**:2608, 1913.

Park, Wm. H.; Zingher, A., and Serota, H. M.: The Schick Reaction and Its Practical Applications, Arch. Pediat. **31**:481, 1914.

Park, Wm. H., and Zingher, A.: Practical Applications Obtained from the Schick Reaction, Proc. New York Path. Soc., October, 1914.

Park, Wm. H., and Zingher, A.: Active Immunization with Diphtheria Toxin-Antitoxin, Department of Health Reprint, Series No. 39, January, 1916.

Blum, J.: Active Immunization Against Diphtheria, New York M. J. **107**: 208, 1918.

Zingher, A.: Active Immunization of Infants Against Diphtheria, Am. J. Dis. Child. **16**:83 (Aug.) 1918.

THE EYE IN HEREDITARY SYPHILIS

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INTRODUCTION

It is a truism that no tissue of the body is exempt from the ravages of syphilis, and as no tissue is exempt, so every organ may be invaded by one or more of the multiform manifestations of this disease. This statement applies equally to inherited as well as to acquired syphilis.

So multifarious and far reaching are the aspects of syphilis, both medical and social, that many master minds have deemed the study of this disease worthy of a life time of intense application. Some of the most brilliant deductions on which our present fairly exact knowledge of the disease is based were made by clinicians prior to the discovery of the spirochaeta pallida. Among the many investigators, two names will go down to posterity as the fathers of modern syphilology — Hutchinson and Fournier.

The knowledge that the eye might be affected in syphilis was known to some of the earliest medical writers. Johannes de Vigo, in "Aphrodisiacus" (1567), speaks of "various diseases of the eye which are caused by lues" and gives therapeutic indications. A cure of "ophthalmia gallica" by means of mercury is described by Zacutus Lusitanus (Amsterdam) in 1634.

It is a far cry from these and other early scattered allusions to the formal exposition of the subject of "Diseases of the Eye of Venereal Origin," which was given to the medical world by William Lawrence in 1830. His treatise has now only a historic interest. In those pre-ophthalmoscopic days the intraocular morbid conditions were little known, and a writer could, without fear of contradiction, give rein to any pleasant fancies he might have.

The first description of pigmented and white atrophic areas of choroiditis as a result of syphilis was given in 1856 by Wordsworth.

Bader[1] (1858) noted the presence of small circumscribed white spots in the eye grounds of a patient who had passed through interstitial keratitis. In 1863, Hutchinson[2] described choroidal and retinal disease in hereditary syphilis, and in 1866[3] he noted the occurrence of optic neuritis in such patients. From this date references to intraocular lesions became each year more and more frequent.

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[1] Bader: Ophth. Hosp. Rep., pp. 248-252, 1857-59.

[2] Hutchinson: Diseases of the Eye and Ear Consequent on Inherited Syphilis, 1863.

[3] Hutchinson: Ophth. Hosp. Rep. p. 307, 1866.

Sidler-Huguenin[4] was able to collate a large number of observations. His paper, which is by far the most exhaustive in the literature, discusses mainly the eye ground changes. He gives a careful summary of papers which have hitherto appeared, supplemented by a very detailed description and classification of the ophthalmoscopic pictures in 125 patients personally observed. Haab[5] has given this aspect of the subject special consideration, and supplements his description of the eye ground changes by several beautiful colored plates. His classification closely resembles that of Sidler-Huguenin. Hirschberg[6] has also considered at length the eye ground changes of hereditary syphilis. Groenouw[7] discusses in a very exhaustive manner, with full references to the literature up to 1904, all the ocular manifestations of hereditary syphilis. As this treatise and the paper of Sidler-Huguenin contain all noteworthy references of the participation of the eye in hereditary syphilis to this date, no attempt will be made to include in the bibliography references prior to 1904.

Allusion should be made to a thesis by Antonelli[8] in which he describes what he terms "Rudimentary Ophthalmoscopic Stigmata" of inherited syphilis. His views, which are presented with great enthusiasm and dogmatism, have received little support, and that mainly from his own countrymen. Sidler-Huguenin, Hirschberg and Haab all speak disparagingly of Antonelli's conclusions. They regard his so-called stigmata either as appearances well within physiologic limits, or representative merely of a vice of nutrition, in which the syphilitic virus may have had an important rôle. They deny in toto that these stigmata are in any sense pathognomonic for syphilis.

OCULAR LESIONS IN HEREDITARY SYPHILIS

The incidence of ocular involvement in hereditary syphilis has been variously estimated. Among 127 cases Rabl[9] found ocular involvement in 39 per cent. Fournier found 48 per cent. of 212 syphilitic children with eye affections. According to the statistics of Ohanian,[10] about 0.5 per cent. of all ocular diseases are caused by hereditary syphilis. His conclusions were based on an examination of 29,528 diseased eyes.

Ocular lesions are rare in the new-born. As a rule, the first signs appear some weeks after birth. The explanation, according to Igersheimer,[11] is that the unborn child usually becomes infected in the last months of intrauterine life. Fetuses which were infected earlier either succumb to the infection before birth or soon afterward. In his series of twenty-seven syphilitic nurslings twenty-one had ocular syphilis.

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[4] Sidler-Huguenin: Beitr. z. Augenh. **51**:1, 1902.
[5] Haab: Ophthalmoscopy, Am. Ed., 1901, Figs. 39, 40, 41.
[6] Hirschberg: Deutsch. med. Wchnschr. **32**:746, 1906.
[7] Groenouw: Graefe-Saemisch., 2d Ed. Pt. 1, **22**:804.
[8] Antonelli: Thése de Paris, 1897.
[9] Rabl: Wien. med. Presse, No. 7.
[10] Ohanian: Geneva Thesis, 1894.

Lids.—The skin of the eyelids may participate in the general cutaneous eruption. Loss of the eyebrows may ensue. It is doubtful whether ulcerative blepharitis ever has a syphilitic basis, although Hutchinson and others have affirmed their belief in this possibility. Inflammation of the tarsus yielding readily to specific treatment has been observed in early infancy. Progressive enlargement of the tarsus is described by Basso [12] in two cases. In one the tarsus had attained the size of a pigeon's egg at the end of the seventh year. The removed mass showed hyaline degeneration of the cartilage and well-marked endarteritis obliterans.

Conjunctiva.—The specific lid eruptions are often accompanied by conjunctivitis. Igersheimer [11] is convinced of the existence of a true syphilitic conjunctivitis, which clears up under general and without local treatment. Hemorrhage from the conjunctiva, sometimes uncontrollable and leading to death, has been observed in infants the victims of hemorrhagic syphilis of the newborn. Syphilitic papules, granulomas, gummas and ulcers may have their seat on the conjunctiva. Essential shrinkage of the conjunctiva may be an end-result of syphilitic pemphigus. In a boy, aged 15, with late hereditary syphilis, Speciale-Cirincione [13] found a conjunctival growth which had all the histologic structure of gumma — perivasculitis with secondary proliferation of connective tissue.

Lacrimal Apparatus.—Infantile dacryocystitis is usually due to blocking of the lower end of the nasal duct with a plug of fetal detritus. However, true syphilitic periostitis of the nasal duct accompanied by specific inflammation of the sac occasionally occurs. Wood [14] examined pathologically the lacrimal glands from ten syphilitic children and found that all bore evidence of disease similar to that found in other glandular organs of syphilitics.

Cornea and Sclera.—The occurrence of parenchymatous keratitis as an incident of hereditary syphilis was known to early writers, some of whom, however, regarded "scrofula" as the most frequent cause of this disease. After Hutchinson had presented his triad of symptoms pathognomonic of hereditary syphilis — misshapen teeth, nerve-deafness, and interstitial keratitis—the latter acquired a greater importance as a diagnostic sign in the eyes of clinicians. Of late years a fourth symptom has been added to the triad, viz., arthritis, which has often been found associated with interstitial keratitis. Thus Puech,[15] in twenty-seven patients with interstitial keratitis, found eleven with joint disease.

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[11] Igersheimer: Ophthalmoscope **11**:718, 1913.
[12] Basso: Ann. di Ottal. **29**:645.
[13] Speciale-Cirincinone: Rev. gén. d'opht. **22**:145, 1903.
[14] Wood: Med. Sentinel **13**:157, 1905.

Can interstitial keratitis occur in the offspring of hereditary syphilitics? In none of the reported cases can one exclude with certainty the possibility of acquired syphilis in the parents or child (extragenital postpartum infection). A well-authenticated case has recently been reported by Strezeminski.[16] On the other hand, Sidler-Huguenin found no syphilitic eye disease in nineteen children of hereditary syphilitic parentage.

Interstitial keratitis has generally been regarded as the most frequent ocular complication of inherited syphilis. Statistics of various authors indicate an incidence of from 6.5 per cent. to 96 per cent. (average in 2,000 cases, 50 per cent.). As is well known, the disease occurs almost exclusively in late hereditary syphilis. Very rarely the cornea is found involved at birth or the disease shows itself in the first days of life (Igersheimer).

The frequent association of keratitis with retinochoroiditis is well established. The time of the occurrence of this complication is usually after the subsidence of the keratitis. It may precede it.

Interstitial keratitis is almost always bilateral, although the eyes are not usually attacked simultaneously. The disease seems to show a slightly greater predilection for females. As is well known, a slight trauma may be the exciting cause. Vigorous specific treatment instituted to cure a unilateral syphilitic keratitis will not usually prevent the development of the disease in the fellow eye or relapses in the eye first attacked. On the other hand, intensive and prolonged treatment of a syphilitic infant prior to the appearance of keratitis will usually prevent its development in either eye.

Very rarely other types of corneal disease have been observed. Groenouw cites Kerabutsi and Outsi,[17] who observed punctate keratitis, and Sendziak [18] who reports sclerosing keratitis. Neuroparalytic keratitis dependent on disease of the trigeminus was noted by Fromaget.[19] Keratomalacia has been observed in very greatly emaciated children. Peltesohn [20] reports two cases cured by specific treatment. Fuchs [21] has recently noted the occurrence of vertically oval cornea in hereditary syphilis. Of twenty-eight cases observed, fourteen had interstitial keratitis. He concludes that vertically oval cornea is relatively more frequent in hereditary syphilis and seems to be the precursor of interstitial keratitis. Distention of the scleral and corneal tissues through increased intraocular tension may lead to megalophthalmos, as in a case reported by Arning.[22]

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[15] Puech: Bull. et mém. Soc. fran. d'opht. **21**:709, 1901.

[16] Strezeminski: Archiv. f. Ophth. **53**:360, 1901.

[17] Kerabutsi and Outsi: Ophthl. Klinik 7:118.

[18] Sendziak: Rev. hebd. de laryngol., No. 2.

[19] Fromaget: Thése de Paris.

[20] Peltesohn: Deutsch. med. Wchnschr. **24**:286, 1898.

[21] Fuchs: Ophth. Rev., London **28**:247, 1909.

Muscles. — Paralysis of the intrinsic and extrinsic muscles and paralysis of the trigeminus have been observed. The oculomotor and abducens may be partially or completely paralyzed. A unilateral internal ophthalmoplegia is almost certainly due to syphilis. Igersheimer has reported eight cases of nystagmus without ophthalmoscopic signs in syphilitic babies; improvement or cure took place under specific therapy. Zappert[23] has observed a complete ophthalmoplegia as the sole manifestation of tardy hereditary syphilis.

Whether or not concomitant strabismus bears any relation to hereditary lues is an undecided question. Antonelli observed squint in 50 per cent. of children with hereditary syphilis. Statistics from other authors indicate a lower incidence.

Iris and Ciliary Body.—Iritis, which was first described as an ocular complication by Lawrence, is infrequent as compared with the occurrence of the disease in acquired syphilis. Sidney Stephenson[24] says: "The disease must be exceedingly rare, for I cannot recall in my work having recognized a single case." It may be present at birth. Owing to the lack of systematic examination of syphilitic infants' eyes, it is probable that we do not, at the present time, know even approximately the true incidence of this disease. Usually of a "quiet" type, it gives rise to few of the classic symptoms and may run its course without the parent suspecting ocular disease. In the absence of marked ciliary congestion and pain, discoloration of the iris and sluggishness or immobility of the pupil are the important diagnostic signs. Not rarely a mydriatic will reveal synechiæ in cases with very slight clinical signs. Serous iritis with deposits on Descemet's membrane has been described. The disease may also simulate the nodular or gummatous iritis of adults. Recently Igersheimer[11] has described what he calls "syphilitic pseudoglioma." A severe plastic inflammation of the iris and ciliary body results in the filling of the pupil with a yellowish mass which soon becomes covered with vessels. This is apt to result in closure of the pupil with secondary glaucoma. A gumma of the ciliary body, appearing as a round red boss 10 mm. behind the corneal margin, has been described by Panas.[25]

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[22] Arning: Deutsch. med. Wchnschr. **36**:289, 1910.

[23] Zappert: Arch. f. Kinderh., **19**:161, 1895.

[24] Stephenson: Ophthalmoscope **4**:506, 1906.

Lens.—Clouding of the lens is for the most part secondary to disease of the uvea or retina. Posterior polar cataract in a syphilitic brother and sister with diffuse retinitis is reported by Riegel.[26] Zonular cataract is stated by Bull [27] to be usually of syphilitic origin.

Vitreous.—Many cases of retinochoroiditis are associated, at least in the beginning, with vitreous haze, which may seriously interfere with vision. Sidney Stephenson [24] describes a form of amblyopia in children due to opacities in the vitreous. The individual particles are usually so small that they cannot be distinguished. Fluctuation in sight is an important diagnostic point. He believes that in children "a cloudy vitreous humor means one thing only — the existence of congenital syphilis."

Eyegrounds.—Disease of the eyeground in hereditary syphilis was first described by Bader [1] and Drognat-Landré.[28] The literature contains a large number of isolated observations, but there was little attempt at classification until the exhaustive treatise of Sidler-Huguenin [4] appeared. This monograph of 256 pages (1902) contains a very complete summary of the literature, together with a detailed account of the general physical and ophthalmoscopic findings in 125 hereditary syphilitics. On the basis of this study this author has divided the retinochoroidal changes in hereditary syphilis into four types, as follows:

Type I: Innumerable fine, roundish, yellowish-red dots, intermingled with equally fine brown or black pigment dots, comparable to black pepper sprinkled over a yellowish red background. This mild form is often present only in one quadrant of the fundus. The peripapillary zone and macula are not often involved. The disk may be normal or pale, but is not atrophic. Vision is usually normal. In more pronounced cases the pigment spots may be large and angular and approach or invade the macula. The nerve is pale — partial atrophy. The retinal vessels are narrowed. Vision is poor. The changes all lie in the retina.

Type II: Larger pigment masses, isolated or confluent, are situated at the periphery. Between these masses are round, reddish-yellow foci which are not so numerous as the pigmented ones. They show little tendency to merge. The disease is situated primarily in

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25. Panas: Arch. gén. d'Opth., 1902.
26. Riegel: Münch. med. Wchnschr. **54**:546, 1907.
27. Bull: Med. Rec. **73**:594, 1908.
28. Drognat-Landré: Ann. d'Ocul., 1875.

the choroid. The nerve may undergo partial or complete atrophy. Sometimes the eyeground between the areas is a leaden hue, traversed by bands of connective tissue. Type II is often found after the subsidence of interstitial keratitis.

Type III: Consists of round or oval, light-colored areas, usually situated at the periphery. They may extend back toward the posterior pole. Some of the areas remain small; others coalesce and become very large. Prolongations may extend toward the posterior pole. Bordered by pigment, the areas themselves may become lightly pigmented. The disease is probably situated for the most part in the choroid. To this type belongs choroiditis alveolaris. Vision is impaired only when the macula is involved.

Type IV: Bears a striking resemblance to retinitis pigmentosa; cannot, indeed, always be differentiated from it. The nerve-head is atrophic, with narrowed vessels. The pigment masses are more rounded and larger than in retinitis pigmentosa, and alternate with yellowish-red and gray-white atrophic spots. The peripapillary zone is leaden hued. Vision and light sense are diminished.

Three colored plates, illustrating, respectively, Types I, II and III, are given by Haab.[5] As his descriptions of these different appearances are very clear, it has seemed worth while to reproduce them. Of Figure 39, representing Type I, Haab has this to say: "The periphery in the lower left-hand portion of the picture presents a leaden hue, and coal-black circular and triangular pigment patches. The rest of the eyeground is covered with minute yellowish-red spots. The yellowish-red rounded spots stand out from the brown dotted background, which looks as if it were sprinkled with snuff. The retinal vessels are rather small and the optic nerve somewhat discolored. Sometimes the sprinkling is found only in the periphery of the eyeground. But whenever this sprinkling is at all well marked, it indicates hereditary lues."

Figure 40, representing Type II, is thus described: "The disease is often confined for a long time to the periphery. . . . The pigment patches are probably, for the most part, situated in the retina, and are caused by a disease of the pigment epithelium. I am unable to decide whether the pale linear and circular yellowish patches are situated in the choroid or in the pigment epithelium. They may be situated in one or the other. This and the following form of the disease are not rarely found after a diffuse interstitial keratitis if, after the cornea has become sufficiently cleared up, the periphery of the eyeground is carefully examined. In some cases the patches may be confined to one side; in others they may be scattered more or less over the entire eyeground and on both sides. In the case here presented there had been a keratitis."

Of Figure 41 he says: "In place of the black and gray patches which predominate both in size and number in the foregoing picture, we find in some cases only whitish, also circular, and often confluent patches. The larger of these are undoubtedly situated in the choroid. This is shown in the figure by the oval white patch traversed by a red vessel. It is a choroidal vessel, hence the choroidal tissue near the vessel is absent and the white of the sclera shows through. There is no doubt, however, that the pigment epithelium of the retina has disappeared at the site of the patches and is slightly increased about their margins, so that the margins appear somewhat darker than the surrounding tissue. This condition also followed an attack of parenchymatous keratitis. Occasionally the forms shown in Figures 40 and 41 are associated, resulting in a mixture of both dark and light circular confluent patches at the periphery, while sometimes in addition we find the form shown in Figure 39, viz., minute red and yellow spots on a brown mottled background, with a sprinkling of small pigment patches. In general, these three types of hereditary specific eyeground disease show a tendency to the formation of spheric foci, which coalesce and form irregular figures."

Most of the intraocular lesions of hereditary syphilis may, according to Hirschberg,[6] be placed in one of the following four groups: First: Anterior hyalitis, consisting of fine, dust-like opacities. Second: The nerve-head is covered with a delicate veil gradually fading into the surrounding retina. Under treatment the veil may disappear, although the nerve-head never regains its "virginal" tint. Some cases recover, but with connective-tissue formation on the disk. Third: The macular region presents a uniformly brown discoloration. Fourth: The fundus is strewn with countless small, light-colored areas, more numerous near the periphery. There is frequently a pigment dot in the center and pigment massing along the border.

It is often a difficult matter, even for the most experienced ophthalmoscopist, to determine with certainty whether a given appearance signifies a pathologic state or is merely a deviation from the physiologic. For instance, the tint and outline of the nerve-head, the course and caliber of the vessels, the color and texture of the macula, the amount and character of pigmentation in the periphery all vary, and sometimes widely, within physiologic limits. What to one observer may have significance, either as a deviation from the normal sufficiently wide to be considered pathologic, or as a special stigma of a constitutional vice, may, to another, be wholly within physiologic bounds.

Whether there exist veritable ophthalmoscopic stigmata of hereditary syphilis or not, there was not wanting an Italian, A. Antonelli,[8] to assert with conviction that such stigmata existed, and to defend his position in a thesis presented before the Faculty of Medicine of Paris. Antonelli believes that certain ophthalmoscopic appearances which ordinarily have been classified as physiologic deviations, have true significance as stigmata of hereditary syphilis. He says: "Les lesions du fond de l'oeil comptent parmi les manifestations les plus frequent de la syphilis congenitale, et que ces signes ophtalmoscopiques sont souvent les seules qu' il soit possible de reconnaitre d'emblee, si l'on est prevenu de la chose et si l'on est assez rompu aux finesses de l'ophtalmoscopie."

Rudimentary ophthalmoscopic stigmata are, according to Antonelli's definition, "lesions which cause no functional disturbance, are not likely to be discovered in the ordinary routine of examination, and are so insignificant that they may readily pass unperceived by the ophthalmoscopist."

These stigmata concern: 1. The color, margins and vessels of the disk. 2. The appearance of vessels as they pass over the disk margin and in the peripapillary zone. 3. Color and pigmentation of the peripapillary and central areas. 4. Alterations in the center, equator and periphery of the eyeground.

The following is a synopsis of these stigmata: The papilla is pale or gray over all, or in sectors; the margin is veiled. A pigment mass ("cadre pigmentaire") bordering the disk is sharply defined on the side of the disk and shades off to the retina. The arteries are narrowed, the veins are full. There are irregularities of caliber. The vessels on and near the disk are partially obscured. In the peripapillary region there exists: (1) Retinal edema, often limited to the space between two vessels; (2) a typical slate color, shading off toward the equatorial region. There may be punctate pigmentation, which, when situated peripherally, bears resemblance to pigmentary degeneration of the retina.

It is not surprising that Antonelli's dicta have failed to find widespread support. Most ophthalmoscopists can hardly bring themselves to regard a choroidal pigment ring or regional obscurations of vessels as significant of syphilis or any other disease. On the other hand, the gray nervehead and the brown punctate pigmentation are appearances that all other observers have noted, and they doubtless have a real significance. A careful critique of Antonelli's work was made by Herbout,[29] who divides these stigmata into two categories: 1. Those which are only modifications of the pigment epithelium — choroidal ring, and slate color of the peripapillary region. They have no more significance than irregularities of pigment distribution in the skin, hair, or iris. They are simply marks of degeneration. 2. Those which are indications of past optic neuritis; pallid disk with obscured borders, narrowed arteries and voluminous veins.

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[29] Herbout: Thése de Paris, 1900.

Disease of the retinal vessels (arteries, veins, capillaries) is indicated by the development of perivascular white lines and eventually by the transformation of the vessels into solid white strands. Retinal hemorrhages or choroidal atrophic areas may be associated with the diseased vessels. Under specific treatment the vessels may be restored to normal. Oliver[30] has described a rare type of perivasculitis in which the arteries and veins were exceedingly dilated. Igersheimer notes the frequency of a pale silver gray tint of the optic disk, which probably is the intraocular expression of a high-grade anemia. One such nerve examined histologically showed neither inflammation nor degenerative changes.

Primary optic neuritis occurs in hereditary as well as in acquired syphilis, and may result in secondary optic atrophy. Heine[31] insists that optic neuritis is very common in syphilitic infants. His material, from Neumann's clinic, indicated that of 105 syphilitic babies, 86 (81.9 per cent.) had optic neuritis. He asserts that optic neuritis may be the sole sign, in addition to a positive Wassermann, of hereditary syphilis, and hence that it has great diagnostic significance. This very large percentage has not been found by other observers. It is questionable whether a primary atrophy occurs. There seems good grounds for believing that tabetic optic atrophy may occur (Lervit[32]).

It is important to note that eyeground changes may escape observation for the reason that usually they give rise to no symptoms. Very rarely is the infant so blind that he cannot grasp at toys and in other ways comport himself as a normal child, so that only by a systematic examination of the eyeground of every syphilitic child will these changes invariably be brought to light.

Orbit.—Periostitis of the orbit, involving, as a rule, the upper part of the orbit, has been noted in hereditary, as well as in acquired, syphilis. Pain and exophthalmos are prominent symptoms. Optic neuritis or choking due to interference with the venous return may occur. Sometimes the process goes on to pus formation. Tumors and tuberculosis of the orbit must be excluded.

Miscellaneous. — Primary glaucoma has never been observed. Increased tension may occur as an incident in the course of retinochoroiditis or iritis. Congenital anomalies, such as microphthalmos,

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30. Oliver: Tr. Am. Ophth. Soc. **11**:265, 1906-1908.
31. Heine: Jahrb. d. Kinderh. **72**:328, 1910.
32. Lervit: Thése de Berlin, 1906.

coloboma of the iris, corectopia, congenital cataract, ectopia lentis, defects of the lens, and choroidal coloboma have been ascribed by some authors to hereditary syphilis.

PATHOLOGY

A consideration of the pathology of the ocular lesions of hereditary syphilis is outside the scope of this paper. A very complete summary, up to 1902, of the rather scanty literature bearing on the pathology of retinal, choroidal and optic nerve lesions is given by Sidler-Huguenin (p. 30). (For a systematic discussion the reader is referred to Parsons, Pathology of the Eye, 1904, vol. i, pp. 5, 78, 191, 278, 294, 354; vol. ii, pp. 406, 434, 461, 615, 683.)

The present study was undertaken to gain some conception of the extent to which the ocular tissues participated in the lesions of inherited syphilis. The work was entered into with an open mind and without knowledge of the results of similar studies which had previously been published

The material came exclusively from the Pediatric Clinic of Washington University and the wards of the St. Louis Children's Hospital. A number of these patients applied primarily to the eye clinic and were referred to the pediatric clinic for diagnosis and treatment. It is believed that the 100 cases fairly represent the types of hereditary syphilis seen in a pediatric service, and that the number and kinds of ocular complications are what might be expected in such a group.

No child was included in whom the clinical diagnosis of hereditary syphilis was not confirmed by at least a 2 plus blood Wassermann. In forty-eight children a spinal fluid Wassermann was made in addition. To the best of my knowledge the present is the only ocular study in which the clinical diagnosis has been confirmed in every case by a serologic test. The examination of each child's eyes was conducted systematically and recorded on a prepared blank, which included the following points to be investigated: 1. Name. 2. Age. 3. Sex. 4. Color. 5. Clinical diagnosis. 6. Localization of syphilitic lesions. 7. General complications (non-syphilitic). 8. Blood Wassermann. 9. Spinal fluid Wassermann. 10. Pupils (size, equality, reactions). 11. Ocular muscles (strabismus; paralytic or concomitant; internal or external). 12. Conjunctiva. 13. Cornea (clear, nebula, leukoma, keratitis, salmon patch, ulcer, vascular remains). 14. Descemet's membrane (deposits). 15. Anterior chamber (clear, cloudy). 16. Iris (color, iritis, synechiæ). 17. Lens. 18. Vitreous. 19. Eyegrounds (disk, arteries, veins, perivasculitis, edema, exudate, hemorrhage, pigmentation, depigmentation). 20. Ophthalmoscopic diagnosis (full description).

Analysis of Eye Findings in One Hundred Cases of Hereditary Syphilis

No.	Age, Yrs.	Sex and Color		Pupils	Muscles	Cornea	Iris	Eyegrounds	B. W.	S. F. W	Clinical Diagnosis	Remarks
1	13	F	W	R. > L., react	....	....	Hazel	R., disk hyperemic, margins veiled; small round clumps of hyperpigmentation alternating with areas of depigmentation; L., the same	+++	—	Hereditary syphilis	V. R. E., 6/5; V. L. E., 6/5; nerve deafness
2	11	M	W	Equal, react	....	Both nebulous from former keratitis	R., gray; L., piebald	R. and L., lower periphery punctate with fine brown dots	+++	—	Latent hereditary syphilis	Eyes very sore at age five
3	9	F	W	Equal, react	....	....	Hazel	R. and L. normal........	++	—	Hereditary syphilis	
4	10 mos.	M	W	R. and L., miosis, react	....	....	Hazel	Both disks pale, margins veiled; retina very pale, vessels narrowed	++++	—	Hereditary syphilis	Square rachitic head; spleen enlarged
5	10	M	W	Equal, react	....	R., nebula below; L., dots of central infiltration	Blue	R., disk veiled above; L., upper and nasal margins obliterated, retinochoroidal spots	++++	—	Hereditary syphilis	V. R. E., 6/8; V. L. E., 6/5
6	8	F	W	L. > R., L. fixed	....	....	Hazel	R. and L., partial optic atrophy, perivasculitis; "peppered" generally; macula presents larger pigment clumps overlying retinal vessels	++++	0	Syphilitic spastic paraplegia	Partial optic atrophy with disseminated chorioretinitis; marked tendency for pigment to wander together in clumps
7	1	F	Col.	Equal, sluggish	....	....	Brown	Both disks pale; irregular peppering tending to clumping	++	0	Hereditary syphilis	Mother states baby's eyes weak in bright light; small and undernourished
8	9	M	Col.	Equal, react	....	....	Brown	R. and L. normal........	++	—	Hereditary syphilis	Subjectively well
9	1½ mos.	F	W	Equal. react	....	....	L., iritis, synechia up	R., disk pale; veiled; arteries narrow; veins full; L., red reflex only	++++	++++	Hereditary syphilis	R., post. neuritic atrophy; L., iritis, hyalitis; died of bronchopneumonia
10	1 mo.	M	W	Equal, react	....	....	Hazel	R., disk pale; veiled; veins full, not tortuous; L., "peppered" fundus, marked at macula; veins full, not tortuous	++++	0	Hereditary syphilis	
11	5	F	W	Equal, react	R., external squint; not paralytic	....	Hazel	R., optic atrophy; L., normal	+++	0	Hereditary syphilis	Rapid lateral nystagmus; at times eyes are quiet; idiocy; carious teeth, pyorrhea
12	5	F	W	Equal, react	....	....	Brown	R. and L. normal...	++++	—	Hereditary syphilis	Pertussis; chronic bronchitis
13	11 mos.	F	W	Equal, react	....	....	Gray	R. and L. normal........	++++	—	Hereditary syphilis	
14	7	F	W	Equal, react	....	R. and L., interstitial keratitis	Brown	R. and L. normal........	++++	0	Hereditary syphilis	Old poliomyelitis; residual paralysis

15	5	M	W	Equal, react	....	R., small infiltration	Hazel	R., disk decidedly pale; L., normal	++++	0	Hereditary syphilis	Premature infant; poor nutrition
16	3	M	W	Equal, react	....	....	Brown	R. and L. normal........	++++	—	Hereditary syphilis	Evidence of former rachitis
17	1	M	W	Equal, react	....	....	Brown	Both disks very much congested; margins veiled	++++	0	Hereditary syphilis	Rachitis
18	2	M	W	Equal, react	....	....	Hazel	Both fundi "peppered"	+++	0	Hereditary syphilis	
19	1	F	W	Equal, react	....	....	Brown	Choroidal rings; uneven distribution of pigment at macula	++	—	Hereditary syphilis	Pulmonary tuberculosis
20	3	F	W	L. > R., L. fixed	....	....	Gray	R., nerve head pale, margins veiled; numerous round masses consisting of a pigment ring surrounding a depigmented annulus; center of each frequently occupied by a gray pigment spot; interpigmented spaces are "peppered"; L. the same	++++	++++	Cerebral syphilis	Hemiplegia
21	9	F	W	Equal, react	....	....	Gray	R., temporal margin of disk and adjacent retina edematous; disk pale; L., the same; in addition, diffuse pigmentation of retina	++++	0	Cerebrospinal syphilis	Hemiplegia, right cortex
22	10	M	W	Equal, react	....	....	Hazel	R., optic neuritis; tortuous veins; L., optic neuritis with peppering lower part of fundus	++	0	Hereditary syphilis	Postpharyngeal membrane
23	11	F	W	L. > R., L. fixed	....	R., temporal nebula; L., small nebula	R., iritis; brown	R., disk atrophic; vessels extremely attenuated; rounded pigment masses in macula; L., chorioretinitis; rounded pigment masses in upper retina; vessels attenuated	++++	—	Hereditary syphilis	Paralytic mydriasis; no other clinical signs
24	8	M	W	Equal, sluggish	R., partial ptosis	....	Gray	R., disk pale; margins veiled; L., disk slightly pale; margins better defined	++++	++++	Cerebrospinal syphilis	Mental deficiency
25	12	F	W	Equal, react	....	R., keratitis; L., old vascular remains	Hazel	R. and L. normal........	++++	—	Hereditary syphilis	Gumma wall of pharynx
26	6	F	Col.	Equal, react	Internal strabismus	....	Brown	L., retinochoroidal atrophy upper part of fundus; R., normal	++++	++++	Cerebrospinal syphilis	

Analysis of Eye Findings in One Hundred Cases of Hereditary Syphilis—(*Continued*)

No.	Age, Yrs.	Sex and Color		Pupils	Muscles	Cornea	Iris	Eyegrounds	B. W.	S. F. W.	Clinical Diagnosis	Remarks
27	6	M	W	R., very sluggish; L., 3.5 mm.; react	....	....	Gray	Optic neuritis; both maculae very granular	++++	++++	Hereditary syphilis	
28	10	M	W	Equal, react	....	....	Brown	R., congested disk; edema of retina to nasal side; L., optic neuritis; several minute retinal hemorrhages	++	0	Hereditary syphilis	Bronchitis
29	6	M	W	L. > R., sluggish	....	....	Brown	R., neuroretinitis punctata; periphery finely "peppered"; L. the same	++++	+++	Cerebrospinal syphilis	Paresis (?)
30	6	F	W	Equal, react	....	....	Hazel	R. and L., "peppered" fundus; R. shows irregular pigment distribution at temporal margin	+++	0	Hereditary syphilis	Pulmonary tuberculosis
31	10	M	W	Equal, react	....	....	Brown	R. and L. normal.........	++++	++++	Cerebrospinal syphilis	Idiocy
32	13	M	W	Equal, react	....	....	Blue	R., temporal pallor, obscuration of nasal half of disk; splotches of retinal pigment around disk, granular macula; L., the same	++++	0	Hereditary syphilis	Orthostatic albuminuria
33	13	F	W	Equal, react	....	....	Blue	R. and L., congested disks; brown punctation in maculae	++++	0	Hereditary syphilis	Slightly feeble minded
34	2	M	W	Equal, react	....	....	Blue	R. and L. macular regions look as though dusted with pulverized pepper	++++	0	Hereditary syphilis	
35	13	F	W	Equal, react	....	R., central scar from exposure	R., iritis	R. and L. normal.........	++++	0	Hereditary syphilis	Large syphilitic ulcer of frontal region; lower eyelid destroyed by ulceration
36	14	M	W	Equal. react	....	....	Hazel	R. and L., marked retinal haze; R., depigmented area bordered by pigment	++++	0	Hereditary syphilis	Gumma of liver
37	8	F	W	Equal, react	....	Both, old interstitial keratitis	Brown	R. and L. normal.........	+++	—	Hereditary syphilis	
38	6	M	W	Equal, react	....	R. and L., nebulae	Hazel; L., iritis	R., upper and lower periphery show a few patches of depigmentation	++++	0	Hereditary syphilis	
39	13	F	W	R. > L.; R., sluggish	....	....	Brown	R. and L. normal.........	++++	—	Hereditary syphilis	L., posterior polar opacity; mental deficiency

40	11	M	W	Equal, react	....	....	Hazel	R. and L., partial optic atrophy	++++	0	Hereditary syphilis	Chronic bronchitis
41	4 mos.	M	W	Equal, react	....	....	Hazel	R. and L. normal.........	++++	++++	Hereditary syphilis	Dermatitis; diarrhea
42	8 mos.	F	Col.	Equal, fixed	....	....	Gray; L., ectropion uvea	R. and L. normal.........	+++	—	Hereditary syphilis	Very rapid nystagmus — about 150 oscillations a minute
43	9	F	W	Equal, react	....	....	Hazel	R. and L., disks very red; fine pigmentary deposits throughout	++	—	Hereditary syphilis	R., ptosis; arthritis of knee; V. R. E., 6/12; V. L. E., 6/5
44	9	M	W	Equal, react	....	R. and L., nebula from old interstitial keratitis	Brown	R. and L., probably normal; corneal haze	+++	—	Hereditary syphilis	Marked rhagades at oral angles
45	9	M	W	Equal, react	....	....	Brown	R. and L., optic neuritis	+++	0	Hereditary syphilis	Osteomyelitis of tibia
46	6	M	W	Equal, react	....	R., central nebula from old keratitis; L., normal	Gray	R. and L., areas of fine-brown punctation alternating with depigmented spots	++	0	Hereditary syphilis	
47	12	F	W	R. and L., marked hippus	....	....	Gray	R. and L., very well-marked choroidal ring; upper part of fundus distinctly peppered; temporal pallor	++++	0	Hereditary syphilis	
48	9	M	W	Equal, react	....	....	Hazel	L., disk very hyperemic, with blurred lower border; R., normal	+++	0	Hereditary syphilis	Large square head; facial asymmetry
49	1	F	W	Equal. sluggish	....	....	Hazel	R. and L., marked peripapillary pigment punctations	++++	+++	Hereditary syphilis	Malnutrition; sores on body; died
50	2 mos.	M	W	Equal, react	....	....	Gray	R. and L., disks slightly pale	++++	0	Hereditary syphilis	Rash on neck, ankles and wrists; epiphysitis; paralysis of both arms
51	9	F	W	Equal, react	....	R. and L., remains of former keratitis	Blue	R., temporally 6 to 8 round and oval areas of retinochoroiditis; L., 15 to 20 areas of retinochoroiditis in temporal periphery	++++	0	Hereditary syphilis	Saddle-nose
52	3	M	W	Equal, react	Alternating squint	....	Brown	R. and L., disks pale; entire fundi as though sprinkled with fine black pepper	+++	—	Hereditary syphilis	Idiocy
53	3	F	W	Equal, react	....	R. and L., beginning keratitis	Hazel	R. and L., optic neuritis; central and peripheral punctate depigmented dots	++++	0	Hereditary syphilis	Arthritis of knee
54	4	F	W	Equal, sluggish	....	....	Brown	L., small area of retinochoroidal atrophy down and in; R., normal	++++	++++	Cerebrospinal syphilis	Mental deficiency
55	1	M	W	Equal, react	....	....	Hazel	R. and L., partial optic atrophy	++++	0	Hereditary syphilis	Papulosquamous eruption

Analysis of Eye Findings in One Hundred Cases of Hereditary Syphilis—(*Continued*)

No.	Age, Yrs.	Sex and Color		Pupils	Muscles	Cornea	Iris	Eyegrounds	B. W.	S. F. W.	Clinical Diagnosis	Remarks
56	8	F	W	Equal, react	....	R. and L., nebula from antecedent keratitis	Brown	Both disks very pale; peripapillary edema below; both peripheries diffusely peppered	++++	0	Hereditary syphilis	Nerve-deafness
57	3	M	W	Equal, react	....	....	Hazel	R. and L. normal.........	++	—	Hereditary syphilis	
58	5	M	W	Equal, react	....	....	Brown	R. and L., marked peripheral peppering	++++	++++	Hereditary syphilis	Rash on trunk
59	1 mo.	M	W	Equal, react	....	....	Hazel	R. and L. normal.........	+++	0	Hereditary syphilis	
60	9	F	W	Equal, react	....	....	Gray	Both nerve heads much blurred and pale	++++	—	Hereditary syphilis	Chorea
61	9	M	W	Equal, react	....	....	Gray	Both eyegrounds show, in upper periphery, numerous brown punctations	++++	0	Hereditary syphilis	Maculopapular eruption
62	2 mos.	F	W	Equal, react	....	....	Hazel	Disks pale, retina very thin, tesselated eyegrounds	+++	0	Hereditary syphilis	Bloody crusts on skin; died
63	2	M	Col.	Equal, sluggish	....	....	Brown	R. and L., nerves completely atrophic; disk surfaces devoid of blood vessels; sclerosis of peripapillary choroidal vessels	+++	0	Cerebrospinal syphilis	Blind
64	7	F	W	Equal, react	....	R. and L., keratitis	Hazel	L., upper temporal vein greatly dilated; R., normal	++	—	Hereditary syphilis	Condition of left supramacular vessels suggests that at one time there had been retinal hemorrhage
65	2 mos.	F	W	Equal, sluggish	....	....	Gray	Both disks pale; papillary and peripapillary edema, veins overfull	++	0	Hereditary syphilis	Spleen enlarged
66	5 mos.	M	W	R. > L., react	Slight divergent strabismus	....	Gray	R. and L., marked veiling of papillae and circumpapillary retina	++	—	Hereditary syphilis	Both lower lids are slightly inverted
67	3	M	Col.	Equal, react	....	....	Brown	Both eyegrounds show marked diffuse pigment punctation	++	++	Hereditary syphilis	
68	7 mos.	F	W	Equal, react	....	....	Gray	R. and L., marked diffuse pigmentation	+++	0	Hereditary syphilis	Skin eruption
69	3	M	Col.	Equal, react	....	....	Brown	R. and L. normal.........	++	—	Hereditary syphilis	
70	4	F	Col.	Equal, react	....	....	Brown	R. and L. normal.........	++++	++	Hereditary syphilis	

71	4	M	W	Equal, react	Alternating strabismus	....	Hazel	R., haze of macula and pale disk; small retinochoroidal spot; "peppered fundus"; L., disk pale and veiled; several retinochoroidal atrophic spots; perivasculitis; thin membrane overlying retinal vessels below	++++	++++	Hereditary syphilis	Remains of hyaloid artery; arthritis right knee
72	2	F	Col.	Equal, react	....	....	Brown	R. and L. normal.........	++++	0	Hereditary syphilis	Syphilids on face
73	6 mos.	M	W	Equal, react	....	....	Brown	R. and L. normal.........	+++	0	Hereditary syphilis	Has no clinical signs; Wassermann made because mother had syphilis
74	1	F	Col.	Equal, react	....	....	Brown	R. and L. normal.........	++	0	Hereditary syphilis	Mother has 4+ Wassermann; had skin rash
75	5	F	W	Equal, react	....	R. and L., scars from old keratitis	Blue	R. and L., marked choroidal pigment rings	++	0	Hereditary syphilis	Conjunctiva congested
76	7 mos.	F	W	Equal, react	....	....	Gray	R. and L. normal.........	++++	—	Hereditary syphilis	Snuffles, palpable spleen rhagades
77	14	M	W	Equal, react	....	....	Brown	Both disks very pale......	++	0	Hereditary syphilis	
78	11	M	W	Equal. react	....	....	Hazel	R. and L., fundus mottled; L., perivasculitis	++	0	Hereditary syphilis	R. and L., anterior hyalitis
79	9	F	W	Equal, react	....	....	Hazel	Disks pale and filled in; Round dense black pigment areas, apparently in retina, in places overlying retinal vessels; macular regions punctate with dark pin-point pigmentation	++++	0	Hereditary syphilis	Extreme nervousness
80	7 mos.	F	W	Equal, react	....	....	Blue	R. and L. normal	+++	0	Hereditary syphilis	
81	5 mos.	M	Col.	Equal, react	....	....	Hazel	Examination unsatisfactory; apparently normal	++++	0	Hereditary syphilis	Eruption on trunk and face
82	11	F	W	Equal, react	....	....	Hazel	Both disks pale; edematous; also peripapillary edema	++++	+	Hereditary syphilis	
83	5	F	W	Equal, react	....	....	Hazel	R. and L. normal.........	+++	0	Hereditary syphilis; latent	
84	3 mos.	M	W	Equal, react	....	....	Hazel	R. and L. normal.........	++	0	Hereditary syphilis	Anal condylomata conjunctivitis
85	6	M	W	R. > L. react	....	....	Gray	Finely granular, probably physiologic	++++	0	Hereditary syphilis	
86	8	M	W	Dilated, equal, sluggish	....	....	Hazel	Both fundus peripheries evenly punctate with dark brown dots	++++	0	Hereditary syphilis	

ANALYSIS OF EYE FINDINGS IN ONE HUNDRED CASES OF HEREDITARY SYPHILIS—(*Continued*)

No.	Age, Yrs.	Sex and Color		Pupils	Muscles	Cornea	Iris	Eyegrounds	B. W.	S. F. W.	Clinical Diagnosis	Remarks
87	1	M	W	Equal, react	....	....	Gray	Both, numerous pigment dots of varying size, alternating with tiny areas of light color	++++	0	Hereditary syphilis	
88	8	M	W	Equal, react	....	R. and L., old scars of keratitis	Brown	Both, peripheral brown and black punctations	++	—	Hereditary syphilis	
89	3	F	W	Equal, react	Nystagmus	....	Gray	R., optic atrophy; several round white circular areas with pigmented center; L., optic atrophy	++++	++++	Cerebrospinal syphilis	Child evidently nearly blind
90	2	F	W	Dilated, very sluggish	Searching movements	....	Hazel	R. and L., optic atrophy	+++	++	Cerebrospinal syphilis	Sees very poorly
91	7	M	W	Equal, react	....	R. and L., remains of antecedent keratitis	Hazel	R. and L., pigment masses of varying sizes and shapes alternating with light areas in upper periphery	++++	—	Hereditary syphilis	
92	9	F	W	Equal, react	....	R., central nebula; L., dense central vascular scar	Hazel L., synechia	R. and L., no view of eyegrounds on account of corneal scars	++++	—	Hereditary syphilis	
93	10	F	W	Equal, react	R., convergent squint	R. and L., nebula from old keratitis	Brown	R. and L., numerous yellow white, round, approximately equal, punctations in periphery	++	—	Hereditary syphilis	Nerve-deafness
94	9	F	W	Equal, react	....	....	Brown	R. and L. normal; myopia	++++	—	Hereditary syphilis; latent	Speech defect
95	8	F	W	R. > L., react	....	....	Gray	R. and L. normal.........	++++	0	Hereditary syphilis	Poorly nourished
96	13	F	Col.	Equal, react	....	R., scars of antecedent keratitis	Brown	R. and L. normal.........	+++	—	Hereditary syphilis	
97	9	M	W	Equal, react	....	....	Brown	R. and L. normal.........	++++	0	Hereditary syphilis	
98	8	M	Col.	Equal, react	....	....	Brown	R. and L. normal.........	+++	—	Hereditary syphilis	Oral ulceration; gum adherent to cheek
99	8	F	W	Equal, react	....	....	Brown	R. and L. normal.........	++	—	Hereditary syphilis	Papular and vesicular eruption
100	6	M	W	Equal, react	....	....	Hazel	R. and L., optic neuritis...	+++	0	Hereditary syphilis	

The original diagram tabulating results contained columns for recording under these 20 headings. It was found possible and desirable, in the interest of brevity, to omit from the final tables the headings "localization of syphilitic lesions," "general complications," "conjunctiva," Descemet's membrane," "lens," "vitreous," and "ophthalmoscopic diagnosis," and to include in a general heading, "remarks," the occasional abnormality which would have been recorded under the omitted headings. In fully one-third of the cases any visual test was impossible on account of the age of the patient, and hence vision was not taken as a routine.

An examination of this tabulation will show that seventy-four of these children presented definite pathologic conditions in one or more of the ocular tissues or some derangement of ocular function. Some of these conditions, such as interstitial keratitis, immobile pupils, optic atrophy, and certain eyeground changes can with assurance be ascribed to the syphilitic virus. Others, such as concomitant squint and pallor of the nerve-head, may depend on some factor other than syphilis. Cases of this character were not included in the group of seventy-four unless they presented, in addition, definite syphilitic ocular lesions.

The age incidence is shown in the following table:

Under one	17	Seven to eight	3
One to two	7	Eight to nine	9
Two to three	5	Nine to ten	14
Three to four	8	Ten to eleven	5
Four to five	3	Eleven to twelve	4
Five to six	6	Over twelve	11
Six to seven	8		

Sex and Color.—There were forty-eight male children, of whom five were colored, and fifty-two female children, of whom nine were colored. The number of colored children is, of course, too small to permit any conclusions as to incidence or localization of syphilitic disease in the eyes in negroes.

Pupils.—Nine patients showed pupillary inequality. In five, R. pupil > L. pupil. In four, L. pupil > R. pupil. In nine patients the pupils barely reacted to light, and in three there was complete fixity. One patient showed marked hippus.

Muscles.—Two patients had convergent, two had divergent, concomitant strabismus. Alternating convergent strabismus was observed twice. Partial ptosis (unilateral) was seen once. A lateral nystagmus was observed in three patients; in two the oscillations were fairly rapid, but not constant; in one the rate of oscillation was at least 150 to the minute and constant. In one patient, a child nearly blind, there were typical searching movements.

Conjunctiva.—In no case was there a primary conjunctivitis. Conjunctival congestion was present only in patients with active keratitis.

Cornea.—Nineteen patients presented evidences of present or past interstitial keratitis. In seventeen the disease was bilateral. The corneal disease was mostly of a mild type. Some patients who presented indubitable nebulæ had been so slightly incommoded that they, or their parents, denied that the eyes had ever been sore. A beginning bilateral keratitis was observed in a white girl aged 3 (No. 53). In No. 35 syphilitic destruction of the lower lid resulted in keratitis from exposure.

Descemet's Membrane.—In no case were deposits or any abnormality observed.

Aqueous.—The aqueous was slightly turbid in two cases of active iritis.

Iris. — Thirty-six patients had brown irides, thirty-seven hazel, twenty gray, and seven blue. There is, in my opinion, absolutely no connection between the color of the iris and hereditary specific infection. Four patients had mild iritis. In two the condition was unsuspected until the mydriatic, used to facilitate ophthalmoscopic examination, disclosed one or more synechiæ. In the other two there was moderate ciliary injection with cloudiness of the aqueous.

In one patient with an absolutely white eye mydriasis disclosed a synechia which represented an antecedent iritis which had never been recognized and had subsided without local or general treatment.

Lens.—The only abnormality noted was in No. 39, who had a small posterior polar opacity. The periphery of the lens was clear and permitted a good view of the normal eyegrounds.

Vitreous.—Nos. 9 and 78 presented a fine haze of the anterior part of the vitreous. No. 71 showed in one eye remains of the hyaloid artery.

Eyegrounds.—In the ophthalmoscopic examination great care was taken to secure as complete a picture of the eyegrounds as possible, which necessitated, in many cases, repeated examinations under mydriasis. The intraocular lesions of hereditary syphilis are so frequently situated peripherally that an examination confined to the region of the disk and macula would have failed to uncover characteristic ophthalmoscopic changes. The greatest difficulty was experienced with infants, who almost invariably cried and struggled when the light was flashed into their eyes. With the head controlled by the assistant, and the arms and legs firmly pinioned by the nurse, it was usually possible to secure a satisfactory examination. After a short preliminary struggle the infant would become interested in the bright light of the electric ophthalmoscope, and perhaps a little hypnotized by it, and the examination would proceed in quiet. To secure a view of the periphery, a flashlight brighter than the ophthalmoscopic light would be held to the right, left, above and below, and repeatedly flashed. This manœuver usually succeeded in causing the eyes to rotate in the desired direction, and afforded a satisfactory view of the outlying regions of the retina.

Fifty-two of these 100 children presented undoubted pathologic eyeground lesions. Thirty-seven showed no intraocular lesion, but in a few of this group ophthalmoscopic examination was impossible on account of the density of the corneal opacity. There remain eleven "borderline" cases, which, while showing certain deviations from the normal, did not, in my opinion, present such indubitable evidences of intraocular pathology as to warrant their being placed in the first group. These "probably pathologic" cases presented such signs as undue pallor of the nerve-head without signs of true atrophy, hyperemia of the nerve-head without evidence of true neuritis, a diffuse haze of the nerve-head and surrounding retina without central or peripheral lesions, and a brown pigmentation of the macula without other ophthalmoscopic stigmata. There was hardly a single pathologic eyeground that did not present lesions of diverse types; in other words, mixed forms predominated. The attempt will be made to describe characteristic changes under appropriate appellations. These changes were:

1. Peripheral, sometimes central, punctate pigmentation.
2. Peripheral, sometimes central, punctate depigmentation.
3. Fairly numerous (10 to 30) small (⅛ to ¼ disk diameter), round, whitish areas bordered by gray pigment, often containing a small pigment dot in the center.
4. Small to large, irregular, retinochoroidal atrophic areas bordered by pigment.
5. Small to large masses of gray pigment, usually peripheral, irregularly disposed, and alternating with depigmented areas.
6. Disseminated retinochoroiditis.
7. Sclerosis of choroidal vessels.
8. Neuroretinitis punctata.
9. Retinal hemorrhages.
10. Optic nerve: (*a*) Papillary haze. (*b*) Pallid nervehead. (*c*) Optic neuritis. (*d*) Optic atrophy.
11. Vessels: Perivasculitis.

1. Peripheral and central punctate pigmentation coincides very closely with Type I of Sidler-Huguenin, and is comparable to Figure

39 in Haab's Atlas of Ophthalmoscopy. Twenty-eight patients presented this picture. Tiny dots of brown or brown-black pigment are strewn fairly evenly over the retina. Sometimes the entire fundus is "peppered" — more frequently the distribution is confined to large peripheral areas. The individual dots are round or irregular in outline, and vary somewhat in size. Between the dots are minute yellowish red spots.

These punctate brown dots are so characteristic that after a few cases have been observed it is hardly possible to confuse this picture with any other. As Haab has pointed out, the normal blond eyeground is often punctate with numerous fine gray dots which might be confused with the appearances just described. A point in differential diagnosis is that the syphilitic lesions can be seen with the inverted image, which is not true of the physiologic dotting. The syphilitic lesions, too, are darker, vary more in size, and are more numerous than the physiologic dots.

2. Peripheral punctate depigmentation. This type was much less common. It was observed in only three patients. It was seen typically in No. 93. The periphery of each fundus presented numerous light-colored or even white circular dots. In this case there was no pigment dotting between the light areas. The fundus seemed to have been "rained" upon. In the other two patients these light-colored dots occupied one portion of the periphery, while the other portions were punctate with brown pigmentation.

3. Small round white areas with pigment center and border. This picture was seen in several patients, associated with brown punctations. In No. 20, a victim of cerebral syphilis and hemiplegia (blood and spinal fluid Wassermann, 4 plus), there were numerous small, round, whitish areas with center and border lightly pigmented. These occupied the center of the eyeground. They gave the impression of being superficially situated, probably in the retina.

4. Retinochoroidal atrophy. Five patients presented large, irregular areas of dark, pigment-bordered retinochoroidal atrophy. These bore a striking resemblance to the single, unilateral or bilateral, peripherally situated areas often observed in adults who have never suspected the existence of an ocular lesion. May not a specific intrauterine choroiditis which runs its course be the explanation of many of these unsuspected lesions in adults?

5. Masses of gray pigment alternating with depigmented areas. This appearance was observed in 4 patients, most typically in No. 91. Each periphery was occupied by several large, approximately round, gray pigment masses, one-half to one disk diameter in size. These overlay the retinal vessels. Between them the retina was greatly deficient in pigment.

6. Disseminated retinochoroiditis was observed in two patients, most typically in No. 51. The temporal half of each fundus was occupied by half a dozen or more round, fluffy white areas of active retinochoroiditis. At the time of observation there was no pigment massing along the borders of the lesions.

7. Sclerosis of choroidal vessels. This rare anomaly was observed in No. 63. The sclerosis was confined to the area immediately surrounding the optic nerve, which was completely atrophic.

8. Neuroretinitis puncta was observed in No. 29. The nerve-head was moderately swollen, with very numerous pin-point, glistening white dots occupying the edematous macula.

9. Retinal hemorrhages. Several minute retinal hemorrhages were observed in No. 28, a patient with well-marked optic neuritis. In No. 64 the condition of the vessels above the left fovea was suggestive of an antecedent hemorrhage.

10. Optic nerve.—(*a*) Papillary haze. It was surprising to observe how frequently the optic nerve-head appeared slightly fogged, an overlying veil just sufficient to obscure the details of the disk and obliterate the clean-cut line of demarcation between disk border and retina. This obscuration occurred in some eyegrounds presenting no other abnormal appearances. (*b*) Pallid nerve-head. Nineteen disks, which presented none of the appearances of true atrophy, were included in this group. All these cases were in marasmic or anemic children; the pale disk was probably the intra-ocular expression of the general anemia. (*c*) Optic neuritis. If reference is made to the statistics emanating from Neumann's clinic, it will be seen that the claim is made that fully 80 per cent. of syphilitic nurslings have optic neuritis. The present series showed optic neuritis in only eight patients, or 8 per cent. A quite common appearance in hereditary, as well as in acquired, syphilis is a brick-red disk, without swelling, obscuration of the margins, or vascular alteration. To classify such a hyperemic disk as an optic neuritis, is in my opinion, a serious error. The diagnosis of optic neuritis in children should not be made unless there are obscuration of the margins, slight swelling, and vascular engorgement. (*d*) Optic atrophy. Eight patients presented signs of optic atrophy. In six the atrophy affected both nerves; in two it was unilateral. Three were partial atrophies, five were total. In one unilateral case the other eyeground was normal. In the other the fellow eyeground was involved, presenting a retinochoroiditis. In all of the cases the arteries were contracted and the lamina cribrosa was invisible.

11. Vessels. (*a*) Perivasculitis was observed in Nos. 6, 71 and 78. In the first two it occurred in eyes with optic atrophy. In No. 78 the eyeground was otherwise normal.

SEROLOGIC TESTS

As has been stated, no patient was admitted to the series who did not present at least a 2 plus blood Wassermann. At the time the ocular examinations were begun, about three years ago, it was customary to make serologic examinations of the spinal fluid only exceptionally, and for the most part only on hospital patients. At the present time the spinal fluid of nearly every syphilitic child is subjected to serologic and microscopic tests. For this reason the series includes only forty-eight spinal fluid Wassermanns, of which sixteen were positive and thirty-two were negative. A positive spinal fluid Wassermann always indicates involvement of the cerebrospinal system.

CLINICAL DIAGNOSIS

Eighty-nine cases were diagnosticated as "hereditary syphilis"; nine as "cerebrospinal syphilis"; one as "cerebral syphilis," and one as "syphilitic spastic paraplegia." Many patients were marasmic. Many developed complicating troubles, such as rachitis, bronchitis, bronchopneumonia, pertussis, poliomyelitis, tuberculosis, orthostatic albuminuria, diarrhea, arthritis, osteomyelitis and chorea. Several were deficient mentally.

The results of this study point very clearly to the need of a systematic ocular examination of every syphilitic child. Such an examination may not have great importance from the standpoint of diagnosis, for in this respect the serologic test stands preeminent, but without it the clinical picture may be incomplete. As many of the eyeground lesions are situated primarily in the periphery, it is imperative that treatment be instituted at the earliest possible moment in the hope of preventing an extension of the process to the peripapillary and macular regions. Even if the lesion be central, the outlook for useful vision will be better if the condition be early recognized and treatment controlled by frequent ophthalmoscopic examinations. If optic neuritis is found, it may be unwise to give arsphenamin or any arsenical preparation, and to rely exclusively on mercury, at least until all inflammatory signs in the optic nerve-head have disappeared.

I am convinced that the dark-brown, punctate pigmentation is absolutely characteristic of the eyeground of a hereditary syphilitic. It must be differentiated from the gray punctation seen in many blond fundi, but this is a matter of no difficulty after a few of the syphilitic type have become impressed on the mind.

That occasionally this intraocular lesion may be the sole expression of inherited syphilis, or if others have existed they have been so insignificant that they have been overlooked, is illustrated by the following case:

A boy of 5 was brought to the hospital with fever and symptoms of meningeal irritation. The father was unable to account for the condition, as the child had always been healthy, and there was no reason to suppose that he had been exposed to contagion of any kind. The clinical diagnosis was meningitis. I saw the boy in consultation and found a perfectly typical dark punctate pigmentation of the eyeground and ventured the opinion that the Wassermann on father and child would prove positive, which was actually the case. The child promptly recovered under neo-arsphenamin and mercury.

I have been on the lookout for this type of eyeground disturbance in adults, but have encountered it only twice: Once in a young man of 21 who showed corneal evidences of an old keratitis, and once in a 50-year-old hyperopic woman who presented no signs and gave no history of either inherited or acquired syphilis.

The virus of syphilis is deadly to young human life. Countless babies die before they have ever had a chance to live, and countless more eke out a miserable existence for a few years and then perish. So it is that very few syphilitic children reach adult life, and so it is that the characteristic intra-ocular lesions only rarely show in adults.[33]

I desire to acknowledge the kind assistance of the resident staff of the St. Louis Children's Hospital and the clinicians attending the Pediatric clinic. I am especially indebted to Dr. Philip C. Jeans, Associate Professor of Pediatrics in Washington University Medical School, without whose enthusiastic cooperation this study would not have been possible.

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[33] Additional references which may be consulted are the following:
Alonso: Ann. de oftal., Mexico **10**:299, 1907-1908.
Antonelli: Ann. de mal. vén. **2**:81, 1907.
Antonelli: Arch. d'Opht. **33**:491.
Antonelli: Arch. d'Opht. **34**:100.
Boas and Ronne: Klin. Monatschr. f. Augenh., 219 (Feb.) 1913.
Bouvret and Chabal: Marseille méd. **46**:424, 1909.
Brecht: Charité-Ann., Berlin **24**:371, 1899.
Brueckner: Ztschr. f. Augenh. **20**:493.
Burch: St. Paul M. J. **11**:577, 1909.
Cabannes: Cong. Internat. de Med., Lisbon, Sec. 11, **15**:340-353, 1906-1907. Gaz. hebd. d. sc. méd. de Bordeaux **30**:421, 1909.
Carbone: Clin. Ocul., Palermo **6**:1991, 1905.
Collins: Polyclin., London **7**:42, 1903.
Derby and Walker: Tr. Amer. Ophth. Soc. **13**:317.
Dimmer: Klin. Monatsbl. f. Augenh., 877, 1913.
Dubar: Echo méd. du nord, Lille **11**:245, 1907.
Falchi: Ann. di Ott., Pavia **34**:928, 1905.
Fournier: Gaz. méd. Sicil. **13**:433, 1910.
Fromaget: Ann. d'Ocul. **143**:244, 1910.
Futagami: Nippon Gank. Zasshi, April, 1914.
Galezowski and Valli: Rev. d'Oph., Par. **3**:429, 1908.
Garcia: Arch. de oft. **13**:396.
Gaucher: Cent. f. prak. Augenh. **36**:93.

Gaucher and Abrami: Bull. Soc. fran. de Dermat. et Syph., Paris **29**:212, 1908.
Gaucher, LaCapere and Weil: Ibid. **15**:15, 1904.
Guignon: Thése de Bordeaux, 1905.
Harmann: Trans. Ophth. Soc. United Kingdom **30**:103, 1909-1910.
Igersheimer: Klin. Monatsbl. f. Augenh., 112, 1911.
Igersheimer: 39th Oph. Cong., Heidelberg, 251.
Ito: Arch. f. Augenh., 722 (Dec.) 1911.
Japha: Deutsch. med. Wchnschr. **37**:543, 1911.
De Jesus Gonzalez: Ann. de Oft., Mexico **10**:339, 1907.
Kerabutsi and Outsi: Ophth. Klinik **7**:118.
Koolner: Ophth. Rev. **31**:64.
La Compte: Ann. d'Ocul. **143**:183.
Lagrange and Aubaret: Arch. d'Oph. **24**:510, 1904.
Lait: Nippon Gank. Zasshi, October, 1914.
Le Conedic: Clin. Opht. **16**:264, 1910.
De Lapersonne: Rev. Neurol. **17**:363, 1909.
Lokteff: Vestnik Oftalmol. **17**:197, 1909.
Von Michel: Ztschr. f. Augenh. **18**:295, 1907.
Natanson: Vestnik. Oftalmol. **27**:626, 1910.
Neuburger: Centralb. f. Augenh. **28**:72, 1904.
Oliver: J. A. M. A. **28**:72, 1904.
Onishi: Nippon Gank. Zasshi, November, 1913.
Parisotti: Riv. ital. di ottal. **3**:261, 333, 1907.
Pich: Cent. f. prakt. Augenh., 30, 1911.
Posey: Ophth. Rec. **22**:158.
Potter: Proc. Royal Soc. Med., 9, Sec. Laryngol., 92.
Price: J. A. M. A. **62**:1545 (May 16) 1914.
Risley: Ophthalmology **4**:617, 1907. Ophth. Rec. **20**:184, 1911.
Rolleston: Ophthalmoscope **9**:321, 1911.
Rollet: Lyon méd. **102**:177, 1904.
Roosa: Post Graduate **19**:850, 1904.
Rubel: Klin. Monatsbl. f. Augenh. **49**:227, 1911.
Scalinci: Riv. ital. di Ottal. **4**:238, 1909.
Schlimpert: Deutsch. med. Wchnschr. **32**:1942, 1906.
Sendziak: Rev. hebd. de laryngol., No. 2.
Silberzweig: Nancy Thesis, 1911.
Spiro: Arch. f. Kinderh. **42**:26, 1905.
Stahli: Arch. f. Augenh. **74**: 13.
Stieren: Ophth. Rec. **20**:339 1911.
Terrien: Gaz. d. hôp. **77**:1229, 1904. Clinique **4**:322, 1909.
Terson: Rev. gén. de clin. et de thérap. **25**:359, 1911.
Tournadeur: Thése de Paris, 1902.
Wicherkiewicz: Przegl. lck., Kraków **1**:24, 1913.
Wilmot: Dublin J. M. Sc. **125**:339, 1908.
Zaun: St. Paul M. J. **15**:178.

A REVIEW OF THE LITERATURE OF SYPHILIS IN INFANCY AND CHILDHOOD

PART I

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THE INCIDENCE OF SYPHILIS

The statement has recently been made [1] that not a single estimate of the prevalence of syphilis in the general population can stand the test of examination. The reason is that no study has represented a fair cross section of society. The majority of the studies have been made among the sick poor and it is obviously unfair to apply such statistics to the general population. Jeans,[2] from a review of the literature, estimated that in the poorer class from 10 to 20 per cent. of adult males and 10 per cent. of married women are syphilitic. Estimates among adults of the better class vary widely. McLester [3] found 18 per cent. of 567 private patients seen in consultation to be syphilitic. Day and McNitt,[4] in a survey of hospital admissions, found that among the well-to-do 6 per cent. had positive Wassermann reactions. This is contrasted with 13 per cent. in the middle class and 20 per cent. in the poor whites during the same time period. Cornell and Stillians [5] found 3.6 per cent. of pregnant women in private practice to have a positive Wassermann reaction, while in charity hospital practice 10 per cent. of the pregnant women had a positive Wassermann. It seems evident that the higher in the social scale the lower the incidence of syphilis. This naturally has a bearing on the frequency of hereditary syphilis.

Jeans,[2] from a review of the literature, concluded that from 5 to 6 per cent. of the living infants of the poorer class in this country have syphilis. The incidence among older children is lower (from 2 to 3 per cent.) no doubt due to the higher death rate among syphilitic infants. Lacapère and Laurent [6] state that in Morocco scarcely 30 per cent. of the inhabitants escape. Lange [7] found 2.8 per cent. of the total number of children admitted to the Frankfurt

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[1] Malzberg: J. A. M. A. **73**:1155 (Oct. 11) 1919.
[2] Jeans: Am. J. Syphilis **3**:114 (Jan.) 1919.
[3] McLester: Am. J. M. Sc. **155**:320 (March) 1918.
[4] Day and McNitt: Am. J. Syphilis **3**:595 (Oct.) 1919.
[5] Cornell and Stillians: J. A. M. A. **72**:551 (Feb. 22) 1919.
[6] Lacapère and Laurent: Paris méd. **8**:422 (Nov. 23) 1918; abstr., J. A. M. A. **72**:280 (Feb. 1) 1919.
[7] Lange: Jahrb. f. Kinderh. **90**:83, 1919.

Children's Clinic to be syphilitic. He states that this is similar to other German statistics. In the same clinic 10 per cent. of the adults were syphilitic.

Wirz[8] found 386 syphilitic children among 9,752 admissions to the Munich Children's Clinic in a twelve year period, an incidence of 4 per cent. He also made a Wassermann survey of 200 school children of whom the history and examination were negative as to syphilis. An incidence of 3 per cent. was found. He refers to Saenger who found an incidence of 6.9 per cent. among the new-born in the Munich Obstetrical Clinic. This incidence became 5.9 per cent. when macerated fetuses were excluded. In the pediatric clinic at the same time only from 2 to 3 per cent. of infants had syphilis. However, in the pediatric clinic the Wassermann test was performed only on suspects while Saenger performed it routinely in the obstetrical clinic. Wirz quotes Pfaundler to the effect that but 43 per cent. of the children born living of syphilitic parents reach the age of 10 years, while the normal percentage to reach 10 years is sixty-nine. On this basis, the 3 per cent. at the school age corresponds to 5 per cent. among the new-born. Wirz also thinks that the finding of syphilis in 3 per cent. of unsuspected school children explains the discrepancy between Saenger's figure of 6.9 per cent. in the new-born and the estimate of from 2 to 3 per cent. in the infants of the pediatric clinic.

RELATION OF SYPHILIS TO INFANT MORALITY

From a compilation of the reports of numerous authors Jeans[2] draws the following conclusions: About 75 per cent. of all offspring in a syphilitic family are infected. In a syphilitic family 30 per cent. of the pregnancies terminate in the death of the child at or before term, a proportion three times that which is found in nonsyphilitic families. Thirty per cent. of all children born alive in a syphilitic family die in infancy, a proportion double that which occurs in nonsyphilitic families. Probably from 25 to 30 per cent. of clinically syphilitic infants die as the result of syphilis. Only about 17 per cent. of all the pregnancies in syphilitic families result in living nonsyphilitic children who survive the period of infancy.

Lange[7] observed 100 syphilitic infants during a ten year period. Of these sixty-seven died; twenty-four of these were brought to the clinic in a moribund condition. One-fourth of the infants who died were breast fed. Fifty-two died of secondary respiratory and intestinal disturbance. In spite of the disappearance of syphilitic manifestations, children withstood even mild infection poorly. There were ten premature births in the group and these constituted 10 per cent. of all premature births. Only one of these infants recovered.

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[8] Wirz: Ztschr. f. Kinderh. **19**:189 (July) 1919.

HEREDITARY TRANSMISSION

Most, but not all, authorities agree that prenatal transmission of syphilis probably occurs in all instances from the mother to the fetus at some time after conception. Wile [9] gives arguments in favor of a resting stage of treponema pallida, which form would make possible paternal transmission. In such a case he thinks the mother's Wassermann reaction becomes positive because of exchange of antibodies with the fetus. He thinks that paternal infection is the commonest mode of transmission. In the discussion of Wile's paper opinions are expressed by Schamberg, Heiman and Pollitzer. In spite of the fact that Pollitzer believes a spore stage probable, he argues against the possibility of paternal transmission. Schamberg thinks this method of transmission possible; Heiman does not. Gaucher [10] reports a case as one of paternal transmission. The father had had syphilis for three years. He was free from symptoms for two years before marriage. At the age of three weeks the baby developed mouth fissures and anal condylomas. Two months after parturition the mother developed two chancres on the left nipple followed by axillary adenopathy and roseola. Routh [11] believes it possible that the ovum may become infected by the granule stage which develops later. Routh explains the diminishing virulence of infection in successive children on the basis of spirocheticidal action of chorionic ferments, these becoming more effective as the treponemas lose their virulence. The diminishing virulence alone would seem an adequate explanation without his theory. In line with the belief of most syphilographers is the observation of Smith [12] that *Trypanosoma rhodesiensi* can pass directly from the blood of the mother to the fetus in experimental animals. In regard to a spore stage of the *Spirocheta pallida,* Noguchi [13] states that his personal experiences with cultivated strains do not justify such an assumption, except for the fact that *Spirocheta pallida* under cultural conditions is one of the most viable organisms. The organism is unable to pass through any bacteria-proof filters, though under favorable conditions they may grow through such filters in the course of several days.

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[9] Wile: J. Cutan. Dis. **34**:645 (Sept.) 1916.

[10] Gaucher: Ann. des. mal. ven. **11**:1 (Jan.) 1916; abstr., J. Cutan. Dis. **35**:389 (May and June) 1917.

[11] Routh: Am. J. Syphilis **2**:484 (July) 1918.

[12] Smith: J. Trop. M. **22**:198 (Nov. 1) 1919.

[13] Noguchi: Am. J. Syphilis **1**:261 (April) 1917.

The behavior of syphilis in plural pregnancies is of some interest. DaCosta and Van der Valk[14] report an instance of twins and one of triplets of syphilitic parentage. Of the triplets, a boy, aged 3 years, has obvious signs; one child died aged 3 weeks without signs, and the third child developed normally. Of the twins, a boy, aged 12 years, has obvious signs, while the twin pregnancy stopped development at the size of an orange. Post[15] cites two sets of twins, all having syphilis. Goldenberg[16] reports the occurrence of syphilis in one of twins and its absence in the other.

Though transmission to the third generation is practically impossible of satisfactory proof, instances of such transmission are reported from time to time. Ash[17] reports a case in which the mother and grandmother of the syphilitic infant had syphilis. The proof is quite unsatisfactory because the father of the baby also had syphilis and the brothers and sisters of the mother were not examined. Murrell[18] reports an instance in which the mother of the infant had syphilis while the father gave a negative Wassermann. The maternal grandparents both had syphilis. The chief fault in this case is that the negative Wassermann of the father means nothing.

THE WASSERMANN REACTION

A review of the various methods of carrying out the complement fixation test for syphilis and their comparative value has not been undertaken. Publications bearing on this subject are very numerous, as are also the proposed methods of carrying out the test. A need for standardization of the test is apparent. A discussion has arisen as to a proper name for the test. Vedder[19] prefers "Bordet-Gengou reaction" for the test now generally carried out; Kolmer[20] prefers to confine the term "Wassermann reaction" to a test with the original technic which is still being used by Wassermann; Gay[21] thinks that Wassermann is entitled to the credit for the development of a novel type of nonspecific fixation of great practical utility. It is quite probable that the common usage of the present will be continued.

All are agreed that the Wassermann reaction, though of great value, should not replace careful clinical examination in any degree. Its value is already so well understood that detailed discussion is not considered necessary. It is generally recognized, that the reaction may be negative in a syphilitic child at birth, and that it becomes positive in the course of a few weeks or months. A strongly positive reaction is present throughout the activity of the disease in childhood. Though the subsidence of activity, with or without treatment, to the point of a negative reaction may and not infrequently does occur, it but rarely occurs in the period of childhood. Several diseases common to this country are reputed to cause positive reactions at times. Tuberculosis is the most frequent example. A serum giving a strongly positive complement fixation test for tuberculosis, because of its high titer and partial nonspecificity, may give a weakly positive Wassermann reaction, especially if a cholesterolized antigen is used. Snow and Cooper[22] found that nonsyphilitic tuberculous individuals may give from partial to complete fixation with cholesterolized antigen in about 31 per cent., but that the percentage giving a positive reaction with noncholesterolized antigen is so small as to be negligible. Complete fixation in the Wassermann reaction is as good evidence of syphilis in the tuberculous as in the nontuberculous.

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[14] DaCosta and Van der Valk: Urol. & Cutan. Rev. **23**:159 (March) 1919.

[15] Post: Am. J. Dis. Child. **12**:364 (Oct.) 1916.

[16] Goldenberg: In discussion of paper of Wile, Ref. 9.

[17] Ash: Am. J. Syphilis **3**:200 (April) 1919

[18] Murrell: Virginia M. Monthly **45**:285 (Feb.) 1919.

[19] Vedder: J. Immunol. **4**:141 (May) 1919.

[20] Kolmer: Am. J. Syphilis **4**:166 (Jan.) 1920.

[21] Gay: J. A. M. A. **73**:901 (Sept. 20) 1919.

Malaria, also, is reputed to cause positive Wassermann reactions. Thompson and Mills[23] claim that the test conducted according to a recognized standard does not give a positive reaction in any stage of malaria. If a positive reaction is obtained it is due to undiagnosed syphilis or to faulty technic.

Graves[24] has shown that the Wassermann reaction on serum obtained after death confirmed the antemortem reactions in 97 per cent. of sixty-eight cases. But 2.5 per cent. of the postmortem serums were anticomplementary.

Rusca[25] states that the Wassermann reaction in human milk paralleled that in the blood, except that weak reactions were obtained in colostral milk.

The value of the provocative Wassermann test has been questioned. Stokes and O'Leary[26] found the test of possible benefit in identifying deep seated visceral, osseous or nervous system syphilis in only 27 per cent. of the cases. Its efficiency rose to 40 per cent. in latent cases and to 70 per cent. in late cutaneous and mucous membrane syphilis. It is least valuable precisely where it is most needed, i. e., in obscure visceral, osseous and nervous system infection. Several patients who remained negative showed a symptomatic Herxheimer reaction. This was notably true in the case of periostitis. In their

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22. Snow and Cooper: Am. J. M. Sc. **152**:185 (Aug.) 1916.
23. Thompson and Mills: Lancet **1**:782 (May 10) 1919.
24. Graves: J. A. M. A. **70**:1751 (June 8) 1918.
25. Rusca: Pediatria **27**:343 (June) 1919.
26. Stokes and O'Leary: Am. J. Syphilis **1**:629 (July) 1917.

hands, the therapeutic test was obviously superior to the provocative. The efficiency of the provocative test was approximately 18 per cent. as compared to an efficiency of 60 per cent. for the therapeutic test. The test does not yet rest on an uncriticizable foundation. They obtained only presumptive and not conclusive evidence of the existence of a provocative effect, and state that at the best the test yields rather a small return for the amount of labor involved. Pollitzer and Spiegel,[27] in a series of 150 cases of treated syphilis of all kinds, did not find a single clear case of provoked reaction while the assumption of cure in all the cases was obviously untenable. In a series of cases temporarily negative, selected as probably not cured, the provocative test failed to indicate the presence of syphilis though the subsequent course of the cases proved that the syphilis was not cured. They regard the test as a useless and often a misleading procedure.

THE LUETIN TEST

The luetin test has been largely discredited though it is still vouched for by its originator. Stokes[28] was able to produce a similar reaction by means of agar. With the exception of one apparently nonsyphilitic case, normal and nonsyphilitic individuals did not react to agar. Positive reactions were obtained in known syphilitics in from 50 to 70 per cent. He interprets both the luetin and agar reactions as colloidal adsorption phenomena in a hypersensitive or labile skin and as not being specific in character. Apparently, the skin is made more sensitive by the administration of certain drugs. A number of observers have shown that potassium iodid increased the reaction. Cole and Paryzek[29] found the reaction positive or intensified not only in patients taking large amounts of potassium iodid but also in a lesser degree in patients taking sodium bromid, potassium nitrate, calcium bromid and sodium iodid. Others have reported similar results. Stillians[30] and other observers think that a positive test is very useful and reliable in the diagnosis of late cases in which the Wassermann is negative. The test cannot be used in determining a cure because not uncommonly it is negative in latent cases.

The facts mentioned would still leave the luetin test a very useful procedure, provided positive results were not obtained in nonsyphilitic patients who were not taking drugs. That positive results may be obtained in the absence of syphilis has been affirmed by Blechmann[31] in children, and by Corper, Gekler and Sweaney[32] in adults. The latter found 47 per cent. of the patients admitted to a tuberculosis sanitarium gave positive reactions.

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[27] Pollitzer and Spiegel: Am. J. Syphilis **3**:252 (April) 1919.

[28] Stokes: J. A. M. A. **68**:1092 (April 14) 1917.

[29] Cole and Paryzek: J. A. M. A. **68**:1089 (April 14) 1917.

[30] Stillians: Interstate M. J. **24**:589 (June) 1917.

[31] Blechmann: Arch. de méd. des enf. **18**:197, 1915.

COAGULO-REACTIONS IN SYPHILIS

That syphilitic serum differs from most other serum in regard to the ease with which it can be precipitated has been recognized by a number of observers. Tests for the presence of syphilis based on macroscopic precipitation have been advanced from time to time during the past ten years. A few of these tests discussed in the recent literature are new, others are modifications of methods formerly proposed. Whatever may be the final status of any of the tests it is apparent from them that a large number of syphilitic serums differ in their composition from the majority of nonsyphilitic serums. That there are no protein changes marked enough or of such a nature as to change the index of refraction from the normal has been shown by Vernes and Marchadier.[33]

The simplest of these tests is one decribed by Bruck.[34] It depends on the observation that the precipitate formed on addition of nitric acid to syphilitic serum does not dissolve in distilled water as readily or as completely as in the case of normal or nonsyphilitic serum. The reports[35] to the present indicate that the test is not specific for syphilis. The percentage agreement with the Wassermann reaction is 75 or more. It is apparently of least value in those instances in which it is most needed, the doubtful and weakly positive Wassermann cases.

McDonagh[36] has advanced a "gel" test which consists of the addition of glacial acetic acid to serum, causing the protein to be thrown out as a "gel." The presence of gel is made still more evident by the addition of a sulphate. McDonagh claims that syphilitic serum contains more protein than normal serum and the particles are larger and more numerous. Strickler[37] concludes from his work with the gel test that, though it is a step in the right direction toward finding a simple chemical test for syphilis, it cannot be compared in accuracy to the Wassermann reaction.

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[32] Corper, Gekler and Sweaney: Am. Rev. Tuberc. **1**:544, 1917.

[33] Vernes and Marchadier: Compt. rend. Soc. de biol. **82**:176 (Feb. 22) 1919.

[34] Bruck: Münch. med. Wchnschr. **64**:25 (Jan. 2) 1917.

[35] Toyama and Kolmer: J. Cutan. Dis. **36**:429 (Sept.) 1918. Smith and Solomon: Boston M. & S. J. **177**:321 (Sept. 6) 1917. Stillians: J. A. M. A. **69**:2014 (Dec. 15) 1917. Corper and Fiala: Am. Rev. Tuberc. **2**:290 (July) 1918. Farbach: Am. J. Syphilis **2**:292 (April) 1918. Terada: Kitasato Arch. Exper. M. **3**:123 (Oct.) 1919.

[36] McDonagh: J. Cutan. Dis. **35**:222, 1917.

[37] Strickler: J. Cutan. Dis. **35**:426, 1917.

The German literature for 1919 contains numerous articles on the "Sachs-Georgi reaction." [38] The test is a precipitation in serum by means of cholesterolized organ extracts. The Meinike reaction [39] is based on the same principles with minor differences in the technic. The technic of the Sachs-Georgi reaction is very simple, but the test is time consuming in that it is not read for from twenty-four to forty-eight hours. In the many articles published there appear but few unfavorable comments on the test. It parallels the Wassermann reaction in from 78 to 94 per cent. The clinical comparison is even better.[40] It is the opinion of some [41] that because of its simplicity and reliability it will probably supersede the Wassermann. Sachs and Georgi [42] found the reaction less sensitive than the Wassermann test in the cerebrospinal fluid but it gives a characteristic qualitative reaction. McCann,[43] working with tests formerly proposed and similar in their nature to the Sachs-Georgi reaction, found that the best results were given by the one proposed by Herman and Perutz. Even this was only partially specific. Between 70 and 75 per cent. of Wassermann positive serums gave positive results, and two of eleven Wassermann negative serums gave positive results.

Kolmer and Toyama [44] describe a coagulo reaction which is very delicate and a constant characteristic of syphilis. The technic is very simple but the test is scarcely practicable because of the difficulty of preparing reagents. The test is based on the observation of Hirschfeld and Klinger that syphilitic serum inhibits or delays the formation of thrombin and consequently of coagulation by an inactivating influence on cytozyme, one of the essential elements in thrombin formation. Uemura [45] reports that this test as elaborated by him is in many cases distinctly superior to the Wassermann.

THE COLLOIDAL GOLD TEST

Practically all writers on the subject agree that the colloidal gold test is of great clinical value. It is the most sensitive indicator we have of pathologic changes in the cerebrospinal fluid. If the colloidal gold reaction is negative, it is highly probable that the Wassermann reaction is also negative.[46] Weston[47] gives a good review of the test with methods and directions and the characteristics of a good solution. The nature of the substance causing the reaction is discussed. Chemically, the test shows the amount of globulin present and indirectly the amount of albumen. The Wassermann reacting substance and the gold precipitating substance are separable constituents.

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[38] Sachs and Georgi: Med. Klin. **14**:805 (Aug. 18) 1918. Georgi: Biochem. Ztschr. **93**:16, 1919. Gaehtgens: München. med. Wchnschr. **66**:933 (Aug.) 1919. Scheer: München. med. Wchnschr. **66**:902 (Aug. 8) 1919. Perutz: Wien. klin. Wchnschr. **32**:953 (Sept. 25) 1919. Lesser: Berl. klin. Wchnschr. **56**:224 (March 10) 1919.

[39] Meinicke: München. med. Wchnschr. **66**:932 (Aug.) 1919.

[40] Löns: Deutsch. med. Wchnschr. **45**:579 (May 22) 1919.

[41] Galli-Valerio: Cor.-Bl. f. schweiz. Aerzte **49**:1977 (Dec. 25) 1919.

[42] Sachs and Georgi: Arbeit. a. d. Inst. f. Exper. Therap. **6**:27, 1919.

[43] McCann: J. Lab. & Clin. M. **4**:742 (Sept.) 1919.

[44] Kolmer and Toyama: Am. J. Syphilis **2**:505 (July) 1918.

[45] Uemura: Am. J. M. Sc. **154**:533 (Oct.) 1917.

SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

There is considerable evidence to show that the nervous system is infected very early in syphilis and it is the general opinion that it is infected only then. As to the frequency of central nervous infection there is no accurate knowledge. Klauder[48] gives a very good review of the situation in regard to acquired syphilis. He cites instances in which the only abnormality is the cerebrospinal fluid early in the disease was the presence of treponema pallida. He thinks it logical to assume that the spirochetes invade the nervous system in every case, and that such invasion may be unaccompanied by laboratory or clinical evidence except the finding of treponemas in the fluid. This assumption is borne out by Warthin,[49] who found in practically every case of latent or clinical syphilis necropsied some degree of thickening of the meninges. The dura was constantly more adherent and thickened, although no active foci were ever found in this membrane. Focal thickening of the leptomeninges were found in practically every case, more frequently in the arachnoid than in the pia. The great majority of these were healed inactive areas. He believes that every case of old syphilis will present some scattered perivascular infiltrations of lymphocytes and plasma cells as are found in all other organs and tissues. These areas represent the local reaction to the presence of spirochetes.

As judged by the examination of the cerebrospinal fluid, a varying proportion of syphilitics show evidence of central nervous involvement depending on the standard set for normal cerebrospinal fluid. Jeans[50] found from a review of the literature that practically one-third of all patients in the early stages of acquired syphilis and an equal number in the later stages showed conspicuous changes in the cerebrospinal fluid, which changes strongly indicated invasion of the central nervous system. He has observed marked changes in the cerebrospinal fluid, including a positive Wassermann reaction, in practically one-third of

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[46] Vogel: Arch. Int. Med. **22**:496 (Oct.) 1918.

[47] Weston: Am. J. Syphilis **3**:266 (April) 1919.

[48] Klauder: Am. J. Syphilis **3**:559 (Oct.) 1919.

[49] Warthin: Am. J. Syphilis **2**:425 (July) 1918.

[50] Jeans: Am. J. Dis. Child. **18**:173 (Sept.) 1919.

214 infants and children with hereditary syphilis. Of those with pathologic cerebrospinal fluids, one-third of the infants and two-thirds of the older children had clinical evidence of nervous involvement. If the assumption is correct that the nervous system is infected in every instance, it is equally logical to assume that spontaneous resolution takes place in about two-thirds of the cases both in acquired and hereditary syphilis. Many writers emphasize the importance of cerebrospinal fluid examination of all syphilitics, especially before they are discharged as cured. Such a routine procedure results in not infrequent surprises.

The pathology and course of hereditary neurosyphilis differs from that of acquired neurosyphilis in but few essentials. Arrest of brain development in any particular is a frequent event in hereditary neurosyphilis,[51] while such an event could not occur in a fully developed adult brain. Meningitis in the pathologic sense is very common in the early stages of hereditary syphilis. Syphilitic involvement of the meninges with definite clinical signs of meningitis is surely not so uncommon as the scattered case reports would lead us to believe. Bly[52] reports one case and cites seven others. Exclusive of these, Hutinel[53] and Snow[54] each report a case. The ages of the patients ranged from 1 to 10 years. Jeans[50] observed seven cases, the ages ranging from 3 months to 4½ years.

There is practically no recent literature on cranial nerve involvement in hereditary syphilis. MacKenzie[55] gives a very good review of the pathology of syphilis of the inner ear and eighth nerve in hereditary and acquired syphilis. In the majority of instances of early hereditary syphilis the meninges are first attacked, the nerve next and eventually the labyrinth. But little is known of the pathology of the later cases. He[56] reports two cases of nerve deafness which completed Hutchinson's triad at the ages of 34 and 44, respectively. Green[57] found optic neuritis or optic atrophy in sixteen of 100 syphilitic infants and children. Klauder[48] states that in acquired syphilis the cranial nerves are involved in the following order of frequency: eighth, second, third, fourth, fifth, sixth and seventh. The involvement is either a neuritis or due to exudate around the nerve. In the majority of instances, in the case of the eighth nerve both the cochlear and vestibular branches are involved bilaterally.

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[51] Wohlwill: Dermat. Wchnschr. **67**:843 (Dec. 14) 1918; Arch. f. Psychiat. **59**:733, 1918.

[52] Bly: Am. J. Syphilis **2**:712 (Oct.) 1918.

[53] Hutinel: Presse méd. **26**:205 (April 22) 1918.

[54] Snow: Am. J. Dis. Child. **16**:161 (Sept.) 1918.

[55] Mackenzie: Am. J. Syphilis **2**:9 (Jan.) 1918.

[56] Mackenzie: Am. J. Syphilis **2**:241 (April) 1918.

[57] Green: Tr. Am. Ophth. Soc. **17**:528, 1919.

The eighth nerve has recently received considerable attention. Instances of marked involvement are relatively uncommon, but minor changes are so common in acquired syphilis even in the very early stages that functional tests of hearing have been considered as possible aids in diagnosis not only of neurosyphilis, but of syphilis in general. Jones [58] states that the eighth nerve, because of its extensive ramifications and its apparent greater susceptibility to toxemia, is the most likely part of the nervous system to be affected. Until recently the degree of function has been determined largely by tuning fork tests which show in syphilitic involvement lowered bone conduction and impairment of hearing for high tones. Goeckermann, Barlow and Stokes [59] found the lowered bone conduction test positive in 78 per cent. of known syphilitics, but also positive in 49 per cent. of nonsyphilitic patients tested. They conclude that because of the high factor of error, the test has only a restricted value as a diagnostic aid in syphilis. Downey,[60] in 1917, reviewed the situation in the very early stages of syphilis.

According to Jones [58] and MacKenzie,[56] these tuning fork tests have their value, but lack the precision and definiteness of the newer tests which are much more delicate and constitute an objective measurement. The degree of function is expressed with mathematical precision. By these tests devised by Robert Bárány the labyrinth is examined. The semicircular canals are stimulated by revolving the person in a turning chair, by douching the ears with either hot or cold water or by applying a galvanic current to the ears. The phenomena produced are nystagmus and vertigo which vary in their degree, duration and direction from the normal. There are no tests of any other cranial nerves which compare in delicacy and accuracy with these tests of the eighth nerve. According to Jones, these tests are very useful in the diagnosis of syphilis and in watching the progress and result of treatment.

As judged from the published case reports, tabes is quite rare as a result of hereditary syphilis. Southard and Solomon [61] report a case in a patient aged 12 years; Lereboullet and Mouzon [62] one in a patient aged 15 years, and Galliot [63] reports two cases at 29 and 36 years, respectively, developing under the stress of the campaign.

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58. Jones: Equilibrium and Vertigo, Philadelphia, J. B. Lippincott Co., 1918, p. 47.

59. Goeckermann, Barlow and Stokes: Am. J. Syphilis **3**:240 (April) 1919.

60. Downey: Am. J. Syphilis **1**:616 (July) 1917.

61. Southard and Solomon: Neurosyphilis, Boston, W. M. Leonard, 1917.

62. Lereboullet and Mouzon: Paris méd. **9**:20 (Jan. 4) 1919; abstr., J. A. M. A. **72**:613 (Feb. 22) 1919.

63. Galliot: Paris méd. **9**:462 (June 7) 1919; abstr., J. A. M. A. **73**:371 (Aug. 2) 1919.

Paresis, though uncommon in hereditary syphilis, is somewhat more frequent than tabes. Ash[64] reports three cases in patients aged 6, 10 and 14 years, respectively. Ricksher[65] reports three cases with the pathologic findings. Southard and Solomon[61] report seven cases and quote previously recorded cases.

On the whole, the result of treatment of paresis in adults has been disappointing. Long remissions have occurred as a result of treatment, and in a few there has been complete arrest as long as followed. Others have had uniformly bad results. Even less has been accomplished with true paresis in childhood. The course is shorter and remissions are rare. The pathology in the child is the same as in the adult.

Valente[66] cites numerous modern authors who do not believe that paresis is due to the direct action of the spirochete, the belief being based, in part, on the fact that spirochetes are not often found in the brain. He cites other observers as having found them in the brains of paretics as follows: Gerber, Benedict and Tater, 4.5 per cent. of twenty-two cases; Marinesco and Minea, 7 per cent. of twenty-seven cases; Noguchi, 24 per cent. of 200 cases; Levaditi, Marie and Bankowski, 27 per cent. of forty-eight cases, and Foster and Tomaczewski 44 per cent. of sixty-one cases. Valente, himself, found spirochetes in 70 per cent. of forty cases, and feels certain that if his search had been continued he would have found them in 100 per cent. Because part of the study was made on living patients, he was often unable to make a sufficiently extensive search. In some of the necropsy material he found enormous numbers in the cortex, more than are commonly seen in the organs in hereditary syphilis.

That some change has occurred in the spirochetes found in paretic brains seems established. Wile and DeKruif[67] found numerous short, thick forms and but few spirals when paretic brain material was inoculated into rabbit testis. They found that cultures grew much more slowly and much less luxuriantly than do those cultivated from early cutaneous and mucous membrane syphilis. Valente[66] inoculated sixty-seven rabbits with paretic brain cortex. None was successful and testicular puncture showed no spirochetes, nor did microscopic examination of the testes show any syphilitic lesions. This was not due to faulty technic, because he was successful with other material. He cites the work of others who were similarly unsuccessful and concludes that in paresis the treponemas must have undergone considerable diminution in virulence for rabbits.

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[64] Ash: Arch. Pediat. **35**:156 (March) 1918.

[65] Ricksher: Alienist & Neurol. **39**:8 (Jan.) 1918.

[66] Valente: Arquivos d. Inst. Bacteriol. **5**:29, 1918.

[67] Wile and DeKruif: J. A. M. A. **66**:646 (Feb. 26) 1916.

That syphilis is a cause of mental deficiency there can be no doubt,[68] though the extent to which it is a cause is in dispute. Kuhlmann[69] found that the frequency of syphilis in the general population runs nearly as high as in the feebleminded. Higgins,[70] on the other hand, found 42 per cent. of fifty mentally defective children to have positive Wassermann reactions, and he quotes the frequency found by other authors as follows: Gordon, 50 per cent. of seventy-five; Fraser, 45 per cent. of ninety-nine; Watson, 60 per cent. of 204. Jeans[50] found that of twenty-five children having clinical evidence of neurosyphilis, twelve had gross mental defect associated.

Hutinel and Nadal[71] observed that acute infections may serve to light up a quiescent hereditary neurosyphilis. They cite a case of syphilitic hemiplegia occurring during measles in a child, aged 4 years. Menninger[72] has noted the same effect in the case of influenza and acquired neurosyphilis.

SYPHILIS OF THE EYES

Green[57] reviewed the literature on the eye in hereditary syphilis and reported his own findings in 100 cases. The incidence of eye lesions in hereditary syphilis has been given by Rabl as 39 per cent. in 127 cases, and by Fournier as 48 per cent. in 212 cases, presumably including all ages of children. Igersheimer found pathology in 80 per cent. of twenty-seven nurslings. Lesions of the lids, conjunctiva, lacrimal apparatus and lens are either rare or secondary to other lesions and are relatively unimportant. Of 2,000 collected cases of hereditary syphilis, keratitis occurred in 50 per cent. A frequent association of retinochoroiditis with keratitis has been observed, usually occurring after the keratitis. A vertically oval cornea has been claimed to be more frequent in hereditary syphilis and to be a precursor of keratitis. Iritis is infrequent as compared to acquired syphilis. Its incidence is really unknown because it is not routinely looked for. A vitreous haze in childhood means hereditary syphilis. It is often associated with retinochoroiditis. Optic neuritis was found by Heine in 82 per cent. of 105 babies. Most of these must have been physiologic variations. Other observers have failed to find such a large number.

In his own study of 100 syphilitic infants and children, Green reports findings as follows: 74 showed abnormality; 9 had fixed or unequal pupils; 4 had strabismus; 1 had ptosis; 3 had nystagmus; 19

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[68] Gaines: Am. J. Syphilis **2**:474 (July) 1918.

[69] Kuhlmann: Journal-Lancet **38**:215 (April 15) 1918.

[70] Higgins: Am. J. M. Sc. **155**:549 (April) 1918.

[71] Hutinel and Nadal: Paris méd. **9**:442 (Dec. 6) 1919; abstr., J. A. M. A. **74**:286 (Jan. 24) 1920.

[72] Menninger: Arch. Int. Med. **24**:98 (July) 1919.

had had keratitis or evidence of past keratitis; 2 had fine haze in the vitreous; 52 had pathologic changes in the eye grounds. There was hardly a single pathologic eye ground that did not present lesions of diverse types, i. e., mixed varieties of involvement predominated. Of those with pathologic eye grounds, eight had optic neuritis; eight had optic atrophy, and twenty-eight had peripheral and central punctate pigmentation. This pigmentation consisted of tiny dots of brown or brown black pigment strewn fairly evenly over the retina. Between the dots are minute yellowish red spots. Three had peripheral punctate depigmentation; 5 showed large irregular areas of retinochoroidal atrophy; 4 had masses of gray pigment alternating with depigmented areas; 2 had disseminated retinochoroiditis; 1 had neuroretinitis punctata; 2 had retinal hemorrhages; 3 had perivascularitis. Green is convinced that the dark brown punctate pigmentation he describes is characteristic of hereditary syphilis. He found this appearance in but two adults, and one of these had scars of old keratitis.

SYPHILIS OF THE EARS

This subject is dealt with at some length under the nervous system. Fraser and Muir[73] describe the pathology of hereditary syphilitic disease of the ear. In young children there exists at present very indefinite knowledge of the changes which occur. From clinical observation it would seem that otitis is very common in syphilitic children. The middle ear symptoms are soon replaced by those of the inner ear. The catarrhal affections developing into a condition clinically corresponding to otosclerosis. The original otitis may possibly be syphilitic, or if pyogenic may progress because of lowered resistance. The microscopic examination in a case of late syphilis is reported in detail.

SYPHILIS OF THE NOSE

No recent observations on the nose in hereditary syphilis have been found. Beck[74] states that the secondary stage of acquired syphilis manifests itself in the nose as an exanthem of macular or papular type. Within the nose these reddish spots frequently become confluent and appear like any other form of coryza. The only way one may differentiate it from simple acute coryza, aside from the presence of spirochetes and the Wassermann reaction, is that the secretion is not marked and the disease is more protracted. Graham[75] describes a peculiar bluish appearance of the nasal mucous membrane in chronic syphilis; also a peculiar sinus involvement and middle ear disease.

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73. Fraser and Muir: J. Laryngol., Rhinol. & Otol. **32**:8 (Jan.) 1917.
74. Beck: New York State J. M. **17**:290 (June) 1917.
75. Graham: Am. J. Syphilis **3**:26 (Jan.) 1919.

TEETH

To properly evaluate changes in the teeth from the normal as a diagnostic aid in hereditary syphilis, it is necessary to know much of the embryology of tooth formation. Such information in relation to syphilis is admirably stated by Stein.[76] The effect of syphilis on the teeth is one of disturbed nutrition which affects the enamel or dentine, or both, of that part of the tooth which is being laid down at the time of the disturbance. According to the literature, such changes are practically never seen in the first teeth, probably for the reason that these teeth have their beginning between the seventeenth and eighteenth week of intrauterine life, and the occurrence of syphilis at that early date in so severe a form as to affect the teeth results in the death of the fetus. In the permanent teeth occur the changes which are commonly known to be associated with hereditary syphilis. These are described in detail by Stein. Syphilis may cause the complete arrest of development of the dentinal germ or follicle, thus resulting in the absence of certain teeth. The absence of certain permanent teeth may result in the persistence of corresponding teeth of the first set, an event which Stein states is more frequent than is generally supposed or recognized. Such persistence of the deciduous teeth is a very important diagnostic sign. It occurs, according to Stein, in the following order of frequency: Second molars, first molars, cuspids, incisors. Not infrequently a fifth cusp is found on the first molar teeth. LaCapere and Laurent[6] find that the presence of this extra cusp has no connection with syphilis.

ALIMENTARY TRACT

Gaucher[77] states that fissuring of the tongue, such as he describes in detail, is a certain indication of acquired or hereditary syphilis.

Tanturri[78] describes a palate sign in hereditary syphilis. The edge of the soft palate as it arches to the uvula has a characteristically irregular outline. It looks dentated, lacelike, instead of a smooth edge, as if eroded. There may be a loss of substance for from 1 to 2 mm. from the edge. The flexibility and color of the palate are not modified. He has observed this sign at all ages, from birth to 20 years, and thinks that it should be accepted as positive testimony of hereditary syphilis.

DeRezende[79] describes an enterocolitis occurring in the new-born as the result of syphilis. The condition usually appears immediately after birth, is characterized by tenesmus and by frequent stools of greenish mucus with or without blood. The infant often screams with pain. Specific treatment without dietary change restores health.

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[76] Stein: Med. Rec. **90**:445 (Sept. 9) 1916.

[77] Gaucher: Ann. d. mal. ven., June, 1917; abstr., Am. J. Syphilis **3**:149 (Jan.) 1919.

[78] Tanturri: Pediatria **27**:4 (Jan.) 1919.

[79] DeRezende: Brazil Medico **33**:297 (Sept. 20) 1919; abstr., J. A. M. A. **73**:1861 (Dec. 13) 1919.

Bauer [80] reports a case of syphilis of the liver with its onset at the age of 11 months. The liver became greatly enlarged, fever was present and jaundice and ascites appeared. Necropsy showed a diffuse hepatitis with intralobular sclerotic atrophy of the parenchyma.

Pentagna [81] reports a case of syphilitic cirrhosis of the liver which began at the age of 24 months. The child had the ascitic fluid withdrawn thirty-one times and died at the age of 34 months. The necropsy showed a Laennec cirrhosis in the hyperplastic stage.

Castex and co-workers [82] have written rather extensively on the gastro-intestinal diseases that occur in adult life as a result of hereditary syphilis. They have observed various bands and kinks, gastroduodenal ulcer and perivisceritis or chronic peritonitis due to inherited infection.

SYPHILIS OF THE LUNGS

Canelli [83] recently gave a fairly complete review of hereditary syphilis of the lungs. According to his statement the condition is frequent and difficult of diagnosis. Often the diagnosis is made only anatomically. The principal forms are gumma, bronchiectasis and pneumonia. The bronchiectasis is primary in some cases. The pneumonias are interstitial, epithelial (desquamative), fibrosclerotic and adenomatous. There may be association of these diverse forms. The pleura rarely is involved. Pulmonary syphilis exists in association with other pulmonary processes, particularly tuberculosis. The histologic changes are complex and multiple. Spirochetes are most frequently found in pneumonia alba.

Plique [84] asserts that the lungs are affected in syphilis with nearly the same frequency as are the bones. It is his opinion that tracheobronchial adenopathy in syphilitic children is generally of syphilitic origin. The late stage of the disease usually appears in the lungs about the fifth year, though it may not appear until adolescence.

Leredde [85] describes twenty cases of acute bronchitis with pulmonary congestion, some presenting emphysema and asthma. The

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80. Bauer: Arch. Pediat. **34**:927 (Dec.) 1917.

81. Pentagna: Pediatria **25**:140 (March) 1917.

82. Castex and Delfor: Prensa méd. Argentina **6**:57 (July 30) 1919; abstr., J. A. M. A. **73**:1810 (Dec. 6) 1919. Castex and Rosso: Prensa méd. Argentina **6**:25 (June 20) 1919; abstr., J. A. M. A. **73**:1169 (Oct. 11) 1919.

83. Canelli: Pediatria **27**:11 (Jan.) 1919.

84. Plique: J. de méd. et de Chir. Pratiques **89**:321, 1918; abstr., Am. J. Syphilis **3**:467 (July) 1919.

85. Leredde: Ann. d. mal. ven. **13**:760, 1918; abstr., Am. J. Syphilis **3**:468 (July) 1919.

lung process was one of syphilitic sclerosis of an active character, a condition which predisposes to other lung diseases. Antisyphilitic treatment may give results not anticipated from the clinical picture.

GENITO-URINARY

Hutinel,[86] writing on nephritis in hereditary syphilis, describes an acute type in two children, aged 19 months and 4 years, respectively, and a chronic type in two children, aged 11 and 13 years, respectively. The nephritis does not assume a special type. The condition is not so much a nephritis as that renal reactions are modified by the specific infection. Uremic manifestations are rare and tardy. He thinks that mercury is not advisable in the treatment of nephritis of syphilis and has witnessed hematuria following its use. He uses arsphenamin intravenously. Rapid improvement or definite cure can be counted on only in the early stage. Because the lesion is restricted to circumscribed regions there is better hope of cure than with ordinary nephritis.

Lange [7] states, from necropsy observation on infants, that kidney syphilis is underestimated because of the small amount of clinical evidence. The changes found were mostly interstitial and delayed development. In prematures and still-births, interstitial changes predominated; in infants, parenchymatous changes (atrophy, cloudy swelling and fatty degeneration). Of his cases, 11 per cent. showed urine changes. Of these, five were specific and six were doubtful. In five cases blood was prominent in the urine. Mercury made none of the patients worse. He states that specific hemorrhagic nephritis was seen three times by Hahn.

Levy and Guilé [87] found spirochetes in the urine of only one of twenty-four men examined near the beginning of the secondary stage. Zimmerman and Levy [88] discovered no striking bladder change on cystoscopic examination of twenty-four patients with acquired syphilis in the secondary stage.

BONES AND JOINTS

Post [89] gives an excellent summary of the bone lesions of hereditary syphilis. However, no new knowledge is presented. Roberts [90] describes a series of cases of hereditary syphilis observed in an orthopedic clinic. In this group there were 81 joint conditions simulating tuberculosis; 17 cases of myositis, some of which presented symptoms usually attributed to sacroiliac strain, 24 cases of arthritis; 8 of disease of the tarsus or carpus; 16 of chronic headaches; 10 cases of osteochondritis of the hip; 1 case of lateral curvature; 33 cases of caries of the spine and 1 case of lymphangitis. Of the total of 226 patients, a Wassermann test was made in forty-seven. The reaction was weakly positive or negative in all. These patients improved with mercury and potassium iodid so remarkably that he argues that either syphilis was a factor in the production of these disorders or else in mercury and potassium iodid we have two remedies whose efficacy has not been fully appreciated.

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[86] Hutinel: Paris méd. **9**:65 (Jan. 25) 1919; abstr., J. A. M. A. **72**:902 (March 22) 1919.

[87] Levy and Guilé: Bull. et mém. Soc. méd. d. hôp. **43**:48 (Jan. 24) 1919; abstr., J. A. M. A. **72**:1332 (May 3) 1918.

[88] Zimmermann and Levy: J. Urol. **3**:407 (Oct.) 1919.

[89] Post: J. Cutan. Dis. **34**:351 (May) 1916.

[90] Roberts: Am. J. Syphilis **3**:587 (Oct.) 1919.

SKIN

Hirschler[91] reported the case of a colored patient, 5 weeks of age, who ten days previously developed vesicular syphilides of the face, hands and feet. The eruption looked like little pearls. He states that a vesicular eruption is one of the rarest of syphilitic manifestations.

Papers on the relation of vitiligo and syphilis are found with considerable frequency in the recent literature. Lane[92] summarized the published knowledge of this relationship. His collected statistics show that from 40 to 50 per cent. of persons with vitiligo, who have been studied in this respect, have been said to have syphilis. He states that it is impossible to arrive at the definite conclusion that there is a relation of cause and effect between syphilis and vitiligo, but the intensive study of the cases is causing this hypothesis to gain ground. Up to the present, no other disease has been demonstrated to be present in anything like this proportion in patients with vitiligo. Ravitch and Steinberg[93] also believe that at present our knowledge is insufficient for definite conclusions. They think that syphilis may be the cause in some cases, but not in all cases of vitiligo.

MISCELLANEOUS OBSERVATIONS

Adair[94] proved syphilis to be present in two of five cases of hemorrhagic disease of the new-born.

Lütjohann[95] reports a case of Raynaud's disease in a 5-year-old girl with auto-amputation of both legs and finally death. He cites eight other cases in the literature, and thinks that the entire disease may be traced to syphilitic changes in the vessel walls.

Costex and Palacio[96] think that hereditary syphilis has a considerable share in the pathogenesis of Banti's disease, aleukemic lymphadenosis in children, paroxysmal hemoglobinuria, chronic hemolytic jaundice with enlarged spleen and glandular disease in the neck in adults.

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[91] Hirschler: J. Cutan Dis. **35**:105 (Feb.) 1917.

[92] Lane: J. A. M. A. **73**:27 (July 5) 1919.

[93] Ravitch and Steinberg: Am. J. Syphilis **2**:479 (July) 1918.

[94] Adair: Am. J. Obst. **78**:678, 1918.

[95] Lütjohann: Monatschr. f. Kinderh. **15**:58, 1918.

[96] Castex and Palacio: Prensa méd. Argentina **6**:105 (Sept. 20) 1919; abstr., J. A. M. A. **73**:1968 (Dec. 27) 1919.

In the syphilitic babies studied by Lange [7] anemia was present in 18 per cent. A decrease in both the hemoglobin percentage and the number of red blood cells was present. No specific blood picture was noted. Both erythroblasts and myelocytes were noted, though the myelocytes were observed only in patients with osteochondritis.

From forty-three necropsies on syphilitic infants, Lange concludes that when the disease is clinically limited to the skin most of the organs were free of syphilis whether the patient was treated or not. He concludes that infants with skin syphilis have a better prognosis than those with visceral syphilis.

Contagion of hereditary syphilis is rare in infants as compared to other infectious diseases of childhood.[97] Werther [98] records ten instances in which nurses had been infected by infants. Steinert [99] records three instances in which wet nurses had been infected, and four instances in which the caretaker had been infected. In the case of the wet nurses the primary sore appeared on the breast, and in the caretakers it appeared in the throat.

A new diagnostic sign for hereditary syphilis has been described by Abrams.[100] The subject faces the west with the feet on a grounded plate and with the hand elevated in proximity to a window. After 30 seconds a circumscribed pallor is demonstrable at the terminal phalanges of all the fingers, notably the little finger, at definite points at the palmar surface of the terminal phalanges and on the inner surface and extreme end.

Valente [101] successfully inoculated rabbit testis with the blood from syphilitics in the primary stage in two cases, and in the secondary stage in three of four cases studied. Neither he nor Uhlenhuth were able to observe spirochetes in the blood which was infectious for rabbits. Uhlenhuth and Mulzer [102] found that blood from cases of early syphilis infected rabbits, but they were unsuccessful in the case of latent and tertiary syphilis. These observations have a bearing on the mechanism of recurrence of syphilitic lesions and on maternal transmission. A view which formerly was held in greater favor than now is that from time to time the blood stream becomes infected from old foci, and that gummatous or other changes result in the areas in which the treponemata are newly deposited. The view more in favor is that a septicemia exists only a single time and that late lesions are due to early implantation and a later lighting up in loco.[9]

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[97] Pfaundler: München. med Wchnschr. **65**:161 (Feb. 5) 1918.

[98] Werther: München. med. Wchnschr. **65**:71 (Jan. 15) 1918.

[99] Steinert: Jahrb. f. Kinderh. **40**:27, 1919.

[100] Abrams: Med. Rec. **94**:103, 1918; abstr., Am. J. Syphilis **2**:803 (Oct.) 1918.

[101] Valente: Arquivos d. Inst. Bacteriol., Camera Pestana **5**:1, 1918.

[102] Uhlenhuth and Mulzer: Berl. klin. Wchnschr. **54**:645 (July 2) 1917.

Warthin[103] presents a new method by which spirochetes may be stained rapidly in tissue sections. Only three days are required, and the results are more certain than with the Levaditi method. Another advantage is that the same paraffin block can be used as for other histologic examination. The stain may be finished twelve hours after the histologic examination of preceding sections shows the desirability of such a stain.

Noguchi[13] discusses the question of immunity of syphilis in considerable detail. Vaccination with dead or avirulent organisms gives no effective immunization. Agglutinins have been demonstrated in rabbits.

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[103] Warthin and Starry: Am. J. Syphilis **4**:97 (Jan.) 1920.

American Journal of Diseases of Children

Vol. 20 AUGUST, 1920 No. 2

THE DUCT SIGN IN MUMPS*

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An epidemic of mumps among the students of the university during the academic year 1914-1915 gave us an unusual opportunity to watch from day to day quite a number of patients sent to the contagious hospital for treatment. Mumps is a disease which is usually seen but once by the attending physician and, very commonly, the diagnosis is made by some member of the family at the time of an epidemic. This may explain why the sign I wish to describe has not attracted general attention. The difficulties in the differential diagnosis of mumps are so slight that it would seem hardly necessary to describe a new sign or one which may have been fully recognized before, but which, as seen by us, has not found its way into the textbooks. There are, however, times when swellings on the cheeks not due to specific parotitis offer some difficulties in diagnosis. The duct sign may prove to be of considerable value in settling the question.[1]

It is a routine practice on my service at the contagious hospital to examine for enanthems as carefully as for exanthems, and to record the findings whether positive or negative, and to note any peculiarities. My attention was called to a red spot on the buccal mucous membrane at the opening of Steno's duct in a case of mumps which entered the hospital Nov. 28, 1914. I did not recall ever having observed any change in the ducts in mumps before this time, and decided to watch for its occurrence in other cases. Since that time, notes have been made on fifty-seven hospital cases, a sufficient number—if the sign has any constancy—to establish it as characteristic of the disease. It is not surprising that this sign has been quite generally overlooked because the spot is so small, is often hidden by the teeth and is usually single. If seen, it would, probably, not excite much attention because of its size. Frequent mention is made of the mouth cavity in mumps in the texts, but it is usually described as being negative.

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* Read at the Meeting of the American Pediatric Society, Highland Park, Ill., June 1, 1920.

[1] Several authors refer to swelling of the mucous membrane at the opening of Steno's duct; Carr: Practice of Pediatrics, 1906; Cotton: Medical Diseases of Infancy and Childhood, 1906; Rochford: Diseases of Children, 1912; Feer: Lehrbuch der Kinderheilkunde, 1914.

Doubtless many have observed this duct involvement and have utilized it as a diagnostic point, but for some reason its significance has been considered so slight that the very large majority of standard texts make no mention of it.

DESCRIPTION OF THE DUCT SIGN

In a case of mumps, if the buccal mucous membrane is well separated from the teeth with a spoon handle and viewed in a good light, the orifice of Steno's duct on the affected side or sides will present a reddened spot measuring from 1 to 2 mm. in diameter. The duct will usually be found to project beyond the surface of the mucous membrane from 1 to 3 mm. In other words, the duct becomes teatulated. The duct is edematous and is usually pale, as a whole, thus accentuating the red central spot which, at times, gives the appearance of a minute ring because of the central opening which may appear darker. In some cases the greater part of the teating is slightly injected. Minute hemorrhagic points may be seen[2] scattered over an area surrounding the duct as great as 2 cm. in diameter. The orifice of the duct is tumefied and from it, at times, may be seen to exude a limpid fluid.

The involvement of the duct is a progressive and retrogressive change. The spot usually appears first and is followed by teatulation with retrogression in the reverse order.

The Red Spot.—The redness varies in shade from a faint pink to a deep inflammatory red; in many cases it never progresses to the deep red stage. As the swelling of the parotid gland recedes, the spot becomes paler and finally disappears. The spot develops early in the disease and, in all probability, precedes in most cases the observable swelling of the parotid gland, as witnessed by the presence of the spot on the unaffected side before the parotid swelling on that side appears (Case 8 [3933]).

The opening of Steno's duct, normally, is more marked in some persons than in others. The slight increased depth of color in such individuals is definitely not inflammatory and is easily differentiated after the duct sign is once seen. In a series of sixty-eight normal persons, children and adults, the duct opening showed a faint but distinct pink color, differentiating it from the surrounding tissues in 14 per cent. of the cases.

The Teatulation.—Under normal conditions, at times, Steno's duct projects beyond the buccal mucous membrane. The opening of the duct, however, is not inflamed and in mumps when such a duct is present, if it is watched closely, it will be seen to undergo a definite change throughout the course of the disease. Teatulation does not always occur. In Cases 9 (4702) and 10 (4733) only the red spot was seen. A careful examination of the ducts in a series of sixty-eight normal persons, children and adults, one or both the ducts projected beyond the mucous membrane in 37 per cent.

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[2] Case 7 (1836) herein described. In one case yellowish spots were observed, Case 2 (1734).

The Duct Pallor.—The duct is usually pale, the pallor so well known in the ordinary mucous membrane swelling of the mouth. At times, this pallor gives the impression of a pale bluish areola surrounding the central red spot.

Duct Congestion or Injection.—This is described in Case 1836. In this case distinct hemorrhages were seen and seemed to be a part of the progressive change. Small hemorrhagic spots on the buccal mucous membrane are not uncommonly seen in children from traumatism—biting the cheeks—and it is possible that this patient may have bitten the projecting mucous membrane. The duct on this side projected fully 3 mm. and the ducts on both sides could be seen to run in between the upper teeth when the cheeks lay against them.

REPORT OF CASES

Case 1 (1550).—Nov. 28, 1914. Male student, aged 22; second day of disease. The patient walked into the hospital. At this time he had swelling and tenderness in both parotid regions. The salivary opening on the left cheek was reddened. Patient had a temperature of 102 F. Later, the temperature reached 104 F. and he had pain in the pelvis which was referred to the testicle next day. No further observations were made in this case.

Case 2 (1734).—March 10, 1915. Student, aged 20; first day of disease. Slight pain at the angle of the right jaw. There was no enlargement of the parotid, but there was slight tenderness on pressure over the angle of the right jaw.

March 11, The left parotid is only slightly reddened. The duct projects 3 mm. The right duct is not red nor does it project; it is flat. The left parotid is distinctly swollen. Patient was discharged on fourth day as a one-sided case of mumps.

March 18. Patient returns. The left duct is now red at the orifice and projects 3 mm. above the surface of the buccal mucous membrane. There is some edema of the duct and surrounding mucous membrane. About the duct on the right side are numerous miliary yellow spots.

March 19. The left parotid is distinctly swollen. Submaxillary glands not involved. Both papillae bulge 2 mm. Only slight redness of duct opening present. The little spots around the right duct are still present.

March 24. Left duct shows swelling, but practically no redness. Highest temperature, 102 F.

Case 3 (1735).—March 10, 1915. Student, male, aged 22; second day of disease. Left parotid much swollen and tender. Right negative. Papillae of both ducts swollen and reddened.

March 11. Both ducts are reddened, particularly the right, and both project 1 mm. above the surface of the mucous membrane. The left opening is faintly seen and slightly dilated. The parotid on the right side is distinctly enlarged, the left only slightly.

March 17. Swelling of both parotid regions has about returned to normal. The opening of Steno's ducts still show slight swelling (tumefaction) more marked on the right. The papillae show a little redness.

March 18. The left duct projects slightly. The center is purplish and very edematous. The anemia around the duct measures 1 cm. in diameter, giving an edematous appearance. On the opposite side the redness has disappeared and the entire buccal mucous membrane appears swollen. The external swelling has almost entirely disappeared on the right side. It is still present on the left side.

March 19. There are dark purplish spots at the center of the duct opening on both sides. The left duct is flat; the right still projects and shows slight edema.

Case 4 (1743).—March 15, 1915. Student, aged 22; second day of disease. Complained of continual aching in right parotid region. Right parotid swollen and tender. Right duct swollen with pinpoint redness at orifice of both ducts. Submaxillaries negative.

March 19. Duct on right side projects an area of 6 mm. in diameter. This area is edematous and has a bluish cast. There is an edematous center seen on the left side but it is not so marked.

March 29. Swelling at duct orifices almost gone, practically no redness. Highest temperature 104 F. Discharged fourteenth day.

Case 5 (1823).—April 30, 1915. Male, aged 19; second day of disease. Examination showed a well developed case of mumps, right parotid. Both papillae were enlarged

May 2. Left parotid swollen. Duct projects. There are three pinpoint openings pointing outward, each showing a distinct reddening. The right duct shows no reddening, it is only swollen. Highest temperature 100 F.

Case 6 (1834). — May 8, 1915. Patient, a nurse, second day of disease, entered contagious service with marked swelling and tenderness of the left parotid and a suggestion of swelling in right. There is no submaxillary swelling. The left duct shows a round bulging which projects from 1.5 to 2 mm. beyond the surrounding mucous membrane. The projection itself is not injected. In the center at the duct opening there is a small reddened depression. The right duct shows a similar picture.

May 11. Both cheeks are now characteristically swollen. The duct of the right side projects about 2 mm. At the center of the duct opening there is a circumscribed deep red point The buccal mucous membrane is edematous, particularly in the space beyond the center of the duct. The red spot at the opening of the duct on the left side, the first involved, is becoming paler.

May 13. Submaxillary glands are now swollen. The patient has been having severe headaches for the past two days. No note on ducts.

May 19. There is still slight swelling of the left parotid. The right duct is negative. The left duct is still slightly elongated. The center is dull red.

May 20. The redness has disappeared and there is no evidence of congestion in the duct region.

Final Note. In this case, what commenced as a mild attack of mumps became complicated on the fourth day with severe headache which was not relieved by medicine and persisted for three days. The temperature reached 102 F. The patient complained of abdominal pain during this time, but we were unable to attribute it to ovarian or pancreatic involvement.

Case 7 (1836).—May 11, 1915. Young woman, aged 20. Two days ago complained of soreness and swelling of right side of face. Yesterday both sides were swollen. This morning the right side shows only slight swelling. The left is characteristic. The right duct is very red at the center, an area of 2 mm. in diameter. There is slight projection or teating of the duct. The left duct projects further, fully 3 mm. The opening is very red and circumscribed about the orifice. Scattered over an area 2 cm. in diameter there are numerous small pointed red spots (hemorrhages) where the buccal mucous membranes are allowed to come against the teeth. The duct runs in between the teeth like a teat about 1 cm. in length.

May 13. Submaxillaries now involved.

May 17. Parotid and submaxillary swellings almost gone. Slight pigmentation of the ducts present.

May 19. Right duct negative. Left is still elongated; there is a dull red spot at the orifice.

May 22. No injection of orifices of ducts or surrounding mucous membranes.

Case 8 (2159).—Dec. 15, 1915. Nurse, aged 23; second day of disease. Examination showed slight swelling of left side of face. Duct slightly enlarged but not red. Next day right parotid swelled.

December 17. Right duct not enlarged or reddened. Left duct projects, orifice slightly red. Highest temperature 103.8 F.

Case 8 (3933).—Jan. 11, 1918. Male student, aged 19; second day of disease. Left parotid swelling marked, tender. There is no swelling of the right side of the face. The left duct is very edematous and inflamed, red. The right duct is only slightly enlarged, pink orifice.

January 22. Since last note the right parotid and duct have been characteristically involved. The swelling on the right side is disappearing while that on the left continues to be smaller and the left duct to be smaller and its orifice red. The right duct is normal.

January 24. Both ducts are normal. Highest temperature in this case, 102.2 F.

Case 9 (4702).—May 7, 1919. A. M., female, aged 26. Patient presents herself at the clinic four hours after she first observed any symptoms, slight swelling of right face. She recalls that at bedtime there was a little soreness in her left cheek. Examination showed the right duct enlarged, projecting and red and the right parotid slightly swollen. Later on the left was involved.

Case 10 (4733).—May 29, 1919. Young woman, aged 23. Two hours after she first noticed soreness and swelling in right jaw. There was difficulty in swallowing. The duct at this time was not swollen, but signs of beginning inflammation of the duct orifice were seen (redness) later on. No further observations were made on this case. This is the earliest primary involvement we have observed. Case 9 (4702) is the next.

Case 11 (5189).—March 29, 1920. Male, aged 19. Came to clinic on the ninth day of the disease. There was marked swelling of both parotids. The left was the first involved. Submaxillaries were negative. Steno's ducts are both teatulated and both orifices are very red. The red area measures 2.5 mm. in diameter. The ducts project 2 mm. Around the reddened areas there is a bluish areola. There are no punctate spots in these areas. The openings of the submaxillary glands are negative.

March 31. Ducts the same.

April 1. Parotid swellings have subsided.

April 3. Ducts: Both orifices are still red, 2 mm. in diameter. There are a few bluish spots in these areas. The redness is becoming less marked.

April 4. Ducts: The redness is much paler; only the orifice itself is now red. Teatulation remains about the same as at entrance. All parotid swellings are gone.

April 5. Ducts: Practically all redness has disappeared. Teatulation the same.

April 10. The ducts do not look so prominent; it is almost impossible to distinguish them.

April 12. Ducts and parotids are entirely negative. Teatulation has disappeared. This was a very marked case of mumps; large swellings of the parotid and marked duct signs. The temperature did not go above 98.6 F. the entire time he was in the hospital, but he entered on the ninth day of the disease.

The fifty-seven cases are here briefly tabulated.

Analysis of Clinical History of Fifty-Seven Cases of Mumps

Case Number	Date	Age	Sex†	Day of Disease First Seen	Teatulation of Duct		Reddening of Orifice		Highest Temperature
					Right	Left	Right	Left	
1550*	11/28/14	22	♂	2	—	—	—	+	102.0
1618	1/17/15	20	♂	2	+	0	+	0	102.0
1683	1/25/15	18	♂	3	+	—	+	—	100.8
1653	2/ 3/15	18	♂	2	+	+	+	+	103.0
1654*	2/ 3/15	20	♂	3	0	+	0	+	104.2
1662	2/ 6/15	18	♂	2	+	+	+	+	99.8
1660	2/ 8/15	22	♂	1	+	0	+	0	99.0
1701	2/24/15	22	♂	1	+	+	+	+	99.0
1697	2/22/15	22	♂	1	+	0	+	0	104.4
1700	2/22/15	23	♂	1	+	+	+	+	101.0
1711	3/ 1/15	18	♂	2	+	0	+	0	98.6
1735*	3/10/15	22	♂	2	+	+	+	+	100.8
1734*	3/10/15	20	♂	1	+	+	+	+	101.6
1743*	3/15/15	22	♂	1	+	+	+	+	103.4
1747	3/16/15	21	♂	2	+	+	+	+	99.0
1765	3/20/15	24	♂	—	0	+	0	+	101.0
1794[1]	4/11/15	23	♂	2	+	+	+	+	102.4
1823*	4/30/15	19	♂	2	+	+	0	+	100.0
1834*	5/ 8/15	21	♀	2	+	+	+	+	102.0
1836*	5/11/15	28	♀	2	+	+	+	+	98.6
1889	6/10/15	5	♂	2	+	+	+	+	Out-patient
2159*	12/17/15	23	♀	2	+	+	+	+	103.8
2421	4/11/16	18	♀	2	+	+	+	+	103.0
3898	12/12/17	21	♂	2	+	+	+	+	104.0
3910	12/14/17	23	♂	12	+	+	+	+	101.8
3933*	1/11/18	19	♂	2	+	+	+	+	102.0
4020	3/18/18	19	♂	2	0	+	0	+	98.6
3989	2/23/18	21	♂	4	0	+	0	+	99.0
3961	2/28/18	21	♂	2	+	+	+	+	99.0
4066*	4/17/18	21	♂	8	+	+	+	+	101.2
3998[2]	5/ 3/18	23	♂	7	0	+	0	+	104.0
4107	5/26/18	Adult	♀	—	+	+	+	+	103.6
0519	6/19/18	Adult	—	3	+	+	+	+	Out-patient
4138	6/21/18	24	♀	2	+	+	+	+	100.2
4193	8/27/18	5	♀	3	+	+	+	+	104.0
4213	9/17/18	33	♂	1	+	0	+	0	100.0
4457	12/27/18	25	♂	2	+	+	+	+	103.4
4490[3]	1/11/19	19	♀	2	+	+	0	0	99.2
4514	1/30/19	19	♀	2	0	+	0	+	99.6
4551	2/18/19	21	♀	2	+	0	+	0	100.0
4578	2/28/19	24	♂	1	0	+	0	+	98.8
4583	3/ 4/19	23	♂	2	+	+	+	+	102.2
4598[4]	3/10/19	20	♂	1	+	+	+	+	98.6
4620	3/22/19	19	♂	2	+	0	+	0	100.2
4630	3/27/19	21	♂	2	+	+	+	+	102.4
4634	3/28/19	22	♂	1	+	0	+	0	99.6
4650	4/ 7/19	21	♂	2	+	+	+	+	102.0
4655	4/10/19	21	—	2	+	+	+	+	100.0
4686	4/29/19	22	♂	1	+	+	+	+	99.6
4701	5/ 6/19	19	♀	1	+	+	+	+	99.8
4702[7]	5/ 7/19	26	♀	1	0	+	0	0	102.2
4714[5]	5/15/19	21	♀	2	+	+	+	0	102.0
4730	5/27/19	24	♀	2	0	0	+	+	100.0
4733[8]	5/29/19	23	♀	2	0	0	+	0	99.0
4753	6/15/19	25	♀	2	+	+	+	+	100.0
4800[6]	7/23/19	14	♂	2	0	0	0	0	99.0
5189*	3/29/20	19	♂	9	+	+	+	+	99.0

* Abstracted in this report.

† In this column, ♂ indicates male, and ♀ female.

1. The discoloration or faint redness of the orifice remained after the swelling disappeared.

2. The parotid swellings had disappeared when this patient entered the hospital for right sided orchitis. The left duct was slightly teatulated. While of interest, this case should not be counted. It simply shows that the duct sign may disappear before the complications of the disease are over.

3. Only one observation was made on this patient by a new intern unfamiliar with the sign. This case should not be considered.

4. A limpid mucus discharge was seen to flow from each duct.

5. The left parotid in this case did not become involved. The slight teatulation may have been normal.

6. A case of submaxillary mumps. The parotids never became involved. There was no reddening of the submaxillary ducts.

7. Observation made four hours after the first swelling of the face was noticed. There had been slight soreness the night before.

8. Observation was made two hours after the patient felt swelling or discomfort in the right jaw. There was no swelling of the ducts. This is the earliest primary case we have observed.

It will be seen that the presence of the duct sign is uninfluenced by the degree of fever. The remarkable involvement of the parotids which may take place in this specific process without an expression in the temperature (Case 11 [5189]) is well known. The same is true of the changes at the periphery of the duct as described above. The sign occurs early in the disease, probably ahead of the parotid swelling in most cases, and persists throughout the course of the disease.

Submaxillary Mumps.—Thus far we have been unable to see any changes in the ducts in submaxillary mumps or parotid mumps in which the submaxillary glands were involved.

Whether the duct sign is pathognomonic of parotid mumps or whether it may occur in any acute inflammatory involvement of the parotid gland, I am unable to say. I have observed a number of face swellings in which the question of mumps arose, two of these acute, in which there was no involvement of the ducts and which later proved not to be mumps.

CONCLUSIONS

1. The duct sign in parotid mumps is described.

2. The duct sign was present in 96 per cent. of the cases recorded and is probably present in all cases of parotid mumps at some time in the course of the disease.

3. Whether the duct sign is pathognomonic of specific parotitis or is present in other acute inflammatory conditions of the parotid gland has not been determined.

4. Because of the occasional occurrence of teatulation of Steno's duct in a certain percentage of apparently normal persons and occasional redness of its orifice, careful differentiation should be made. The duct sign should be regarded simply as corroborative evidence of parotid gland involvement.

ACUTE CEREBROCEREBELLAR ATAXIA

WITH REPORT OF CASES *

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Five years ago I reported an instance of acute cerebellar ataxia, and reviewed the cases occurring in children, so far as examination of medical literature had brought them to my notice.[1] Since that time three other cases have come under my care. An occurrence as frequent as this, although undoubtedly dependent in some measure on coincidence, is certainly an indication that the disease is not as uncommon as we would suppose from the scanty reference to it in medical literature, and in most textbooks on diseases of children. The conviction of the existence of this apparently unsuspected frequency is the motive for the present communication.

Encephalitis is, as is well known, of not uncommon occurrence. In most cases, the large brain bears the brunt of the attack; but it is perfectly possible for the cerebellum to share in the process, or even to exhibit the chief symptoms. It is doubtful whether the process is limited to the cerebellum in any case. Certainly, as far as published case records go, symptoms pointing to involvement of the cerebrum also have always been observed. It is equally true that in the large majority of cases of acute hemorrhagic encephalitis cerebellar symptoms are absent.

What relation the lethargic encephalitis bears to other varieties of encephalitis is a matter which only time can solve, and cannot be discussed at length in this connection. The peculiar prominence of lethargy and asthenia seen in that disease is not characteristic of the majority of cases of other forms, and yet may occur in any of them, as S. Kinnear Wilson [2] pointed out. One of the instances of cerebellar ataxia which I have to report strongly suggests lethargic encephalitis.

REPORT OF CASES

Following are the histories of the four cases, with comments on them; the first case, already published, is abstracted for the sake of completeness. In view of my former communication on the subject, any complete discussion of etiology and diagnosis would be repetition.

Case 1.—Susie R., aged 5 years; negative family and personal history; was taken ill Jan. 4, 1915, with cold in the head and cough. Influenza was prevailing in Philadelphia at the time. The symptoms continued several days, the child

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* Read at the Annual Meeting of the American Pediatric Society, June, 1920.

[1] Tr. Am. Ped. Soc. **27**:234, 1915; Am. J. M. Sc. **151**:24, 1916.

[2] Lancet **2**:7, 1918.

being still out of bed. January 6, she was put to bed with fever and coated tongue. January 10, the temperature was normal, and the child was out of bed and apparently convalescent. January 12, vomiting occurred repeatedly; patient returned to bed complaining of pain in hip. She had now a jerking, irregular speech; the mind was clear. January 13, she was scarcely able to stand; irregular movements of eyes and eyelids; seemed dazed and later in day could not sit unsupported; attacks of screaming. Taken to the Children's Hospital January 14.

On entrance the mind was not entirely clear; speech very jerking and irregular, and only a few words could be said, and these with great difficulty. High degree of lateral nystagmus; knee jerks increased; decided incoordination of muscular movements; no fever. January 15, the mental condition was nearly normal; speech improved, but trembling; nystagmus marked; no paralysis; very decided ataxia of upper extremities. Could stand only when supported, and with feet far apart. Improvement went on very rapidly, and by January 23, nine days after admission to the hospital, could sit in bed unsupported. Nystagmus and ataxia of the arms were still present; some ataxia on standing, and the gait, when supported, showed apparent weakness and uncertainty. February 1, eighteen days after admission, there was still some difficulty in balancing herself when standing or walking; nystagmus was generally absent. The psychic condition had changed from sluggishness, haziness and dulness to alertness and brightness. The temperature has been afebrile while in the hospital. The examination of blood, urine and spinal fluid gave practically negative results.

Comment.—This case was an interesting instance of encephalitis involving apparently preponderatingly the cerebellum. That the cerebrum also shared in the process was indicated by the disturbed psychic state. The cause was not certainly discoverable, but there seemed good reason to consider influenza as the factor. An article by Heiman [3] discusses the subject of the relationship of encephalitis to influenza, as it applies to children, and reports a number of cases. None of them would appear to have been of the cerebellar type. At least, the presence of incoordination is not mentioned. Mills and Wilson [4] reported a case, probably dependent on influenza, and strongly resembling in some particulars that of Susie R.[4]

CASE 2.—Anna P., aged 4¾ years. Father said to have had a bad cough; otherwise the family history was negative. The patient had had no previous illness, except an attack of disturbance of the bowels and of whooping cough at the age of 2 years, and the mother thought she had not seemed entirely well since then. Two weeks before entering the Children's Medical Ward of the Hospital of the University of Pennsylvania, March 24, 1916, it was noticed that the left upper extremity seemed to have impaired power, and that she shook when she tried to use it. It was stated also that on one occasion she complained of being dizzy, staggered a little, and fell down the porch steps, but that she was not unconscious. That evening at the supper table she dropped her fork from the left hand. No more dizziness occurred; there had been no headache, and never any trouble in talking. The entire history of this sudden attack was rather vague. Apparently the first symptom was the momentary staggering and the falling down the steps, followed that evening by the ataxia of the arm. A day or two later the gait became uncertain, she "went to the left side when walking," and had to hold on to objects to keep from falling.

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[3] Am. J. Dis. Child. **18**:83 (Aug.) 1919.

[4] Arch. Neurol. & Psychiat **1**:567, 1919.

On admission to the hospital the patient was found well developed and well nourished; there was no paralysis of any extremity. The movements of the left hand were ataxic. The knee jerks were prompt, and no changes in other reflexes or in cutaneous sensibility were found. The patient stood with swaying and with the feet apart, and the gait was staggering, now to one side, and now to the other. There was no nystagmus, vomiting, or headache. Examination of the blood and urine on this date gave negative results. By April 1 the gait and station were much improved. The child could now stand without swaying, and could walk and even run without staggering. The ataxia of the upper extremity was unchanged.

Shortly after this date the patient developed scarlet fever and was removed to the Philadelphia Hospital for Contagious Diseases.

Nothing further was heard of her until brought at my request to my office, Dec. 29, 1919—three and three-fourths years after the attack. She seemed to be normal in nearly every way, except that there was distinct ataxic movement of the left hand in an effort to touch the tip of the nose, and slight swaying of the left arm in the effort to pick up a pin. On attempting to drink water from a glass held in the left hand, there was some tremor and unsteadiness. The mother thinks there is a slight dragging of the left foot when she tries to skip; but no difference in the movements of the two lower extremities could be detected at my examination.

Comment.—There would appear to have been no illness occurring immediately before the encephalitis developed, but it is possible symptoms really had been present but had not been observed. In any event, they could not have been severe. The suspicion of an unrecognized poliomyelitis of the ataxic form naturally arises, but, on the whole, this seems unlikely. The epidemic of that year had not commenced at the time; the early symptoms were almost too insignificant; the knee jerks were active, and there was no evidence under observation of any actual loss of power. Contrary to the condition of the first case, there was no nystagmus or affection of speech, and although these, it is true, are not characteristically cerebellar in origin, they are often associated with cerebellar disease. There was also no psychic disturbance. There was, however, a characteristic staggering gait and ataxia of the arm. The condition described as a "lack of power" was without doubt an evidence merely of ataxia, since no loss of power could be detected on examination at the hospital. The "shaking" on attempting to use the arm may have been really a tremor, although there was none of this while under observation, but ataxia merely.

Case 3.—Anna G., admitted to the Children's Hospital of Philadelphia, Nov. 22, 1916, aged 6 years. The family history was negative, and the previous personal history was unimportant until the occurrence of a very severe attack of measles, from which the patient suffered in July, 1916. From this she was supposed to have recovered completely; but the truth of this is questionable, since in August internal strabismus was noticed by the mother, and a little later it was observed that the child staggered when she walked. It was found, too, that she had become very backward and had difficulty in talking, and that at times she seemed to be dizzy. The symptoms were believed to be becoming worse.

Examination on admission showed the face blank and expressionless; decided mental apathy; very marked unresponsiveness; convergent strabismus;

constant lateral nystagmus. The gait showed a tendency to go to the left, and the child to fall in this direction. There seemed to be no actual loss of power. Examination of the eyes by Dr. Shumway showed no lesions of importance. Spinal puncture gave a normal fluid. The reflexes were normal. The Baranyi test applied by Dr. Isaac Jones indicated a lesion of the upper posterior portion of the pons and the adjacent anterior superior portion of the cerebellum. An affection of the labyrinth was excluded.

December 5.—On this date, two weeks after admission to the hospital, there was little evidence of ataxia, but still distinct swaying when the eyes were closed. The child now walked well, but unsteadily. There was no ataxia of the arms.

The later history before she left the hospital showed a gradual improvement. The examination of the blood and urine gave no important results; the Wassermann reaction was negative; the von Pirquet faintly suggestive. The child talked but little to the physicians and nurses, but did to all the children, although her speech was slow and jerking. At one time a slight paralysis of the right side of the face seemed to be present, but this soon disappeared, and it was not certain that the observation was correct. The patient continued to be apathetic and to take little notice of her surroundings. The internal strabismus and the nystagmus and affection of gait persisted; but her mother, who saw her for the first time February 6, two and a half months after admission, thought that her eyes were a great deal straighter ,and that the improvement in walking and talking was remarkable. The child left the hospital the next day.

She was readmitted to the hospital Nov. 2, 1917, nine months after her discharge. The staggering gait had apparently for a time been recovered from, although the nystagmus still persisted. Three weeks previously she had commenced to vomit, at first occasionally and then daily; and she then commenced to stagger again. Examination showed the child with slight mental retardation; internal strabismus shifting from eye to eye; slight lateral nystagmus of the left eye; the knee jerks were active but other reflexes normal. The principal complaint at this time appeared to be an inflammation of the tonsils and of the glands of the neck, from which she recovered in a few days. No further later history has been obtainable.

Comment.—The influence of the infectious diseases in producing encephalitis is well known. In this case there seems to be no question that the disorder followed an attack of measles. I have known this to occur in other cases. The inflammation clearly involved the cerebrum, as shown by the persistently affected mental state. That the cerebellum shared in the process seems equally indubitable. The combination of nystagmus and staggering gait leaves open scarcely any other conclusion.

Case 4.—Alice W., aged 3½ years. Seen in consultation with Dr. Malcolm Council, April, 1919. The child had always suffered from chronic intestinal indigestion, and was of a highly neurotic disposition. Under careful treatment she had improved, although she was still subject to attacks from time to time, characterized by insomnia, accumulation of gas in the intestine, mucous stools, and increased nervousness. The family maintained that the child had grippe a short time before the attack of encephalitis which began April 2, 1919. On this day, without apparent reason, she vomited, became constipated, and then semi-stuporous, and her temperature rose to 100.5 F. On the next day, she had her first convulsion, and after this she had convulsive attacks at intervals of from 4 to 5 minutes, during which she stiffened and arched her back in the position of moderate opisthotonos. The attacks were of but a few seconds duration, and there was no rigidity at other times. During all this period she was in a very stuporous condition.

When seen by me the next day, April 3, there was persistent coma. Several of the convulsive attacks were observed, during which the child occasionally cried out. There was no taché; no rigidity, except during the convulsive moments, and no hyperpnea. The condition was supposed to be a toxemia of some sort, similar to that previously experienced, but with new and much more severe symptoms. On this account free purgation was advised, and enteroclysis with soda solution ordered.

I visited her again on April 5. The convulsive attacks had now ceased—they had lasted 60 hours in all—and the bowels had been freely purged; but the mental condition was unchanged; coma had continued, and no word had been spoken. Fever had persisted, the temperature reaching 102 F. The pulse was slow, hard and full. Inasmuch as the symptoms slightly suggested a meningitis, a lumbar puncture was made, but the fluid obtained was clear and absolutely sterile. There was still an entire immobility and absence of speech, and the child was usually much relaxed, with features somewhat sunken, and with occasional slight cyanosis. Most of the time the child was disposed to sleep, and even at the best was more or less soporose. April 8: There had been decided improvement, the patient having become fretful and restless. Although much of the time soporose, it was possible to rouse her and to arrest her attention for a moment.

Recovery advanced very slowly. The child did not speak at all for five months, and then began to say a few words such as "boy," "cow," "yes," and the like. She slowly regained the power of voluntary movement, moving first the arm, and later rolling the head. As muscular movements increased there was a remarkable degree of incoördination noted, all movements being entirely undirected. It was late in August, 1919, before she walked perfectly and talked well, although even then speech was slow. A year after the attack she showed further improvement, but still talked slowly.

Comment.—The cause and nature of this case are not entirely clear. The family lived in the country, and the patient had not been in association with other children. There had been no illness in the house. At the same time it is to be noted that the affection occurred toward the close of the epidemic of influenza in 1918-1919, and that the family are confident that she had had an attack. It is also noteworthy that the symptoms bear in many respects a very decided resemblance to those of lethargic encephalitis, the coma, immobility, and asthenia being very striking features, although there was no evidence of paralysis of any of the cranial nerves. Whether or not the case is to be included in this category is uncertain, but it seems to be very probable. The condition suggests in some respects the cases of epidemic stupor described by Batten and Still,[5] their four cases exhibiting early and persistent stupor, and during convalescence a slow, hesitating speech.

The interesting feature is, that in addition to the involvement of the cerebrum, which was by far the most marked, very decided incoordination was observed during convalescence, pointing to an involvement of the cerebellum as well.

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[5] Lancet **1**:636, 1918.

CONCLUSIONS

The conclusions to be derived from the cases now reported, and from those previously collected from medical literature, may be formulated as follows:

That there is a condition not common, but still certainly more frequent than ordinarily supposed, in which an acute hemorrhagic encephalitis involves the cerebellum, and which could be designated "acute cerebellar encephalitis."

That with this are always combined symptoms indicating an involvement of the large brain as well, and the title "cerebrocerebellar encephalitis," or "cerebrocerebello-bulbar encephalitis," is consequently to be preferred. The degree to which the process involves one or another part of the brain varies with the case; in some instances the cerebellar lesions predominating, in others the cerebral; but in all in the category of cerebellar encephalitis there is, as stated, a combination of the symptoms affecting both regions. In very many more instances the cerebellum escapes entirely, so far as symptoms indicate; but to these no reference is made here.

The cause of this cerebrocerebellar encephalitis varies decidedly. In the majority of the cases previously reported in medical literature, some infectious disease had preceded the attack. This was true of two of my own cases, but no such connection could be discovered in the other two. Among the symptoms oftenest to be seen are:

1. Unconsciousness, usually of but short duration, although this was observed in but one of my own cases.

2. Ataxia, a constant symptom in all instances.

3. Affection of speech, shown sometimes as a complete inability to speak which may last for months; in other cases manifestly an ataxia of speech rather than a mental disturbance. More or less involvement of speech was present in three of my four cases.

4. Disturbance of mentality, apart from unconsciousness, is seen in many instances. It was present in three of my cases. It is usually temporary, but may be very persistent.

5. Nystagmus was observed in two of my cases, and has been reported in a number of others. It is an interesting confirmatory symptom when it exists, but would appear oftener to be absent.

6. "Loss of power" is often a very evident symptom, at least in the observation of the families. It is, however, usually absent, and is probably nearly always dependent in reality on an ataxia. In a few instances, as in my fourth case, there has been a decided hypotonia for a time.

7. Active tendon reflexes are often observed. The knee jerks were increased in two of my four cases, and active in one.

Among other symptoms may be mentioned vertigo, which is conspicuous by its absence. However, the early age at which the majority of cases occurred rendered the determination of the existence of vertigo difficult. Two of my patients had complained of feeling dizzy. Whether this was actually vertigo or not is uncertain.

The consideration of the prognosis is of interest. As far as life is concerned it would appear to be good. Only one of the patients in my first report died, and that was years later. This has prevented an exact study of the pathologic lesions. That the patients will not have clinical evidences of the disease persisting is, however, always uncertain. My first patient recovered absolutely; the second was left with a slight incoordination persisting more than three years after the attack; the third exhibited nine months later slight mental retardation and some remains of the cerebellar symptoms; the fourth had apparently recovered four months later, except that speech was still slow. It is possible that final disappearance of all symptoms may take place in all of them, inasmuch as in a case reported by Taylor [6] there were still symptoms discoverable three and one-half years after the attack, but none twenty years later. Of the seventeen cases collected from medical literature in my earlier report, complete recovery is known to have taken place in a considerable number, and it is probable that this was true of a number more. So far as statistics go, it would appear that the disease will leave no traces in the majority of instances.[6]

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[6] Lancet **2**:1416, 1904.

STUDIES ON THE EFFECT OF DIPHTHERIA ON THE HEART *

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INTRODUCTION

During the course of the acute infectious diseases in childhood, certain changes in the heart muscle are prone to occur, due to the action of the specific toxins. In diphtheria these changes are more or less characteristic. It is my purpose to describe how these changes may give rise to clinical manifestations, and how diphtheria is related to the problem of chronic disease. The study is based on eighty cases that have been under observation in the St. Louis Children's Hospital. The electrocardiographic studies have been made in the Heart Station of the Washington University School of Medicine.

PATHOLOGY

In diphtheria pathologic changes occur throughout the body, particularly in the highly specialized tissues, such as cardiac muscle, nerve, kidney and liver. These changes have been described by Hayem,[1] Babes,[2] Romberg,[3] Councilman, Mallory and Pearce,[4] and others. The changes have been produced experimentally by Welch and Flexner.[5] They are caused by the action of the specific toxin of diphtheria, though the end reaction is similar to that which occurs from other toxins.

The changes consist of two processes: (1) a destructive parenchymatous degeneration of specific cells, occurring generally throughout the body, but particularly in the heart, nerve tissue, kidney and liver, and (2) a proliferation of interstitial tissue with round cell infiltration, representing an attempt at repair in the damaged tissue.

The lesions of the heart muscle may be diffuse or localized, and may occur in the walls of the ventricles or of the auricles, or they may involve the impulse conducting system. The cells show a parenchymatous degeneration, at times with an excess of fat. Occasionally

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* Read before the Section on Diseases of Children at the Seventy-First Annual Session of the American Medical Association, New Orleans, April, 1920.

[1] Hayem: Arch. de physiol. **3**:81, 1870.

[2] Babes: Arch. f. path. Anat. u. Physiol. **119**:460, 1890.

[3] Romberg: Deutsches Arch. f. klin. Med. **48**:369, 1891.

[4] Councilman, Mallory and Pearce: Boston, 1901.

[5] Welch, W. H., and Flexner, Simon: Johns Hopkins Hosp. Bull. **3**:17, 1892.

the cells are fragmented. This lesion may be fatal rapidly or it may pass into a chronic stage in which one sees attempts at repair and healing. In such hearts proliferation of interstitial tissue with round cell infiltration may be seen replacing the destroyed muscle cells. The end result is a fibrous myocarditis. In a certain number of hearts, an increased number of eosinophil cells is present in the muscle.[6] These cells are not found with constancy in myocarditis caused by other infections, and it is probable that they represent some specific reaction, the nature of which is at present unknown.

There is a small group of cases in which it may be difficult to demonstrate any anatomic change, either gross or microscopic, in the heart muscle. This is true even when the clinical picture of heart failure has been well defined, and may occur during the acute stage of diphtheria or in cases in which the clinical diagnosis of myocarditis or myocardial insufficiency, caused by this disease, had already been made.

The great importance of these changes lies in the fact that normal muscle is destroyed and replaced by relatively inert tissue. The total cardiac muscle mass is reduced, and the physiological efficiency is diminished ,the extent depending on the amount of muscle destroyed. The heart is left with its reserve power either very much impaired or entirely gone.

SYMPTOMS

Symptoms associated with these changes usually appear during convalescence, though they may become apparent during the course of the acute infection. They are symptoms of acute cardiac failure. Common complaints are more or less intense dyspnea, the distress depending largely on the amount of dyspnea present, and, at times, precordial pain, cough or pain referable to the liver region. There is usually a moderate degree of fever.

PHYSICAL SIGNS

On examination there is found a varying degree of increase in cardiac dulness; the cardiac impulse and heart sounds are weak; the rate is rapid, and there may be cardiac arrhythmia. At times the rate is as slow as forty, and gallop rhythm may be present. The second pulmonic sound is accentuated. The pulse is weak, thready, rapid and irregular in volume and force. There is pulmonary and general visceral congestion and a moderate degree of cyanosis. There may be some edema.

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[6] Nuzum, Frank: Eosinophilous Myocarditis in Diphtheria, J. A. M. A. **73**:1925 (Dec. 27), 1919.

Electrocardiographic Study.—Clinical evidence of damage to the heart may be observed by electrocardiographic studies. These show disturbances located either in the intrinsic conducting system, or in the heart muscle. Disturbances located in the conducting system lead to delay in the conduction of the impulse from auricles to ventricles, or there may be heart block, either partial or complete. The block may vary in its location and produce either a sino-auricular block, an auriculoventricular block, or may be beyond the bifurcation of the bundle of His in the branch of the conducting system leading to either the right or the left ventricle. Disturbances situated outside the impulse conducting system, such as paroxysmal tachycardia, auricular flutter and auricular fibrillation have been observed. Premature contractions are frequently noted, especially premature auricular contractions. Another very common change is some alteration in the form of the ventricular complex of the electrocardiogram. The amplitude of the waves may be decreased, the duration of the Q R S group of waves is prolonged, and very commonly the T wave becomes iso-electric, diphasic or inverted.

CASE REPORTS

From examinations made on eighty cases in this study, we were able to make a clinical diagnosis of myocarditis or myocardial insufficiency in nineteen. This diagnosis was made by the signs found on physical examination, together with the disturbances observed in the electrocardiogram. Seven of these cases have been selected as examples illustrating the effects of diphtheria on the heart.

Case 1. (Children's Hospital No. 14242)—An infant, aged 10 months, was admitted to the hospital, June 9, 1919, with the history of pharyngeal diphtheria beginning June 5; was given 8,000 units of antitoxin on admission. The membrane was extensive, covering almost all the buccal and pharyngeal mucous membrane as far as could be seen. The general condition was fair, although the child was rather toxic. There were no signs of any cardiac involvement, but the pulse rate was very rapid.

Electrocardiogram [No. 2624]. (Fig. 1).* The first tracing, made June 11, 1919, shows no evidence of muscle preponderance. The Q R S time is 0.080 second, a slight but not abnormal delay; the Q R S complexes are abnormal in Lead I, and low in amplitude in all leads. In this curve it is impossible to measure the S T time, but it seems to be delayed. The T wave is upright and normal. The ventricular rate is 128.6 per minute; the P R time is 0.160 second.

Interpretation: There are slight delays in intraventricular conduction, and moderate disturbance of myocardial function.

Her condition remained unchanged until June 13, when she suddenly became cyanosed, and was in acute distress with dyspnea; examination of the heart revealed very few signs indicating cardiac failure.

Electrocardiogram [No. 2626]. (Fig. 2).—The second record was made June 13.

Interpretation: This record shows very abnormal curves, there being tachycardia of ventricular origin with complexes that suggest an impulse arising from multiple foci in the ventricles. At times these contractions occur at a rate of 177.3 per minute. No normal complexes can be seen, and there is no evidence of auricular activity.

The patient became worse and died about two hours after this record was obtained. No necropsy was allowed.

CASE 2. (Childrens' Hospital No. 15181).—A girl, aged 3 years, was admitted to the hospital Feb. 10, 1920, with a history of onset of pharyngeal diphtheria six weeks before. Antitoxin, 5,000 units, was given three days after the onset and two days later 10,000 units were injected. The throat soon improved and after a week was pronounced well. Two weeks after this, it was noticed that the child walked with difficulty, and this difficulty increased until she was not able to walk at all. She had had difficulty in swallowing for several days previous to her admission. On admission, there was extensive paralysis of the extremities, eye muscles, muscles of deglutition and of the diaphragm. Cyanosis was present; the pulse was irregular and thready; the heart was dilated 4 cm. beyond the nipple line, and the sounds were indistinct.

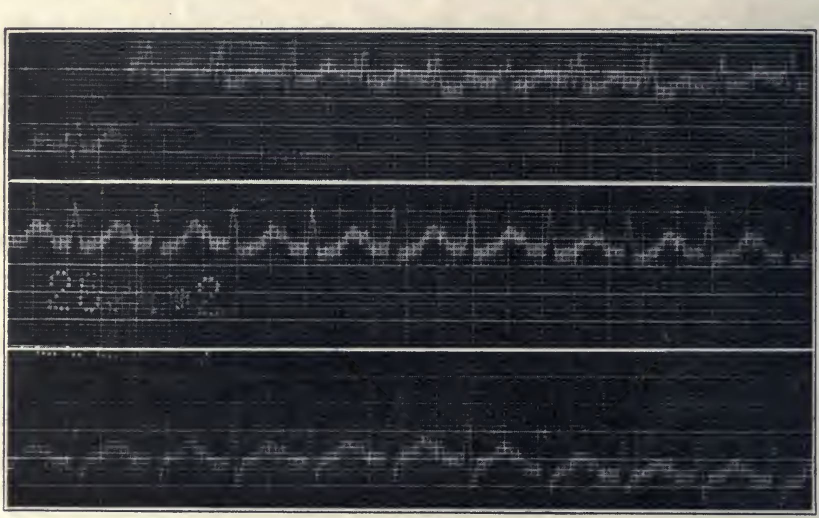

Figure 1

Electrocardiogram [No. 3563].—(Fig. 3).—This was made Feb. 10, and shows normal cardiac mechanism, with premature contractions arising in the right ventricle and marked left ventricular preponderance. The Q R S time is from 0.080 to 0.100 second, which in these curves seems to be a considerable delay; otherwise, the complex is not abnormal. The S T time cannot be measured. The T wave is very low in all leads and it seems to be diphasic. The ventricular rate is 166.7 per minute; the P R time 0.120 second.

Interpretation: There are present marked left ventricular preponderance; possibly some disturbance in intraventricular conduction, and right ventricular

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* The curves in each of the figures except Figures 14, 15 and 16, are those of Lead I, II and III, Lead I being above, Lead II in the center and Lead III below. The curves read from left to right, and were taken under standard conditions.

premature contractions. The girl showed no signs of improvement and died twelve hours after admission. No necropsy was allowed.

Case 3 (Children's Hospital No. 14294).—A girl, aged 4 years, was admitted to the hospital June 25, 1919, with a history of pharyngeal and laryngeal diphtheria setting in June 22. She was given 11,000 units of antitoxin on admission. Her general condition was fair. The heart was not enlarged, the apex impulse was strong; the rate was 128 and no murmurs were detected. Intubation was performed June 27 for cyanosis and dyspnea and resulted in considerable relief. At this time the heart was not dilated or clinically abnormal.

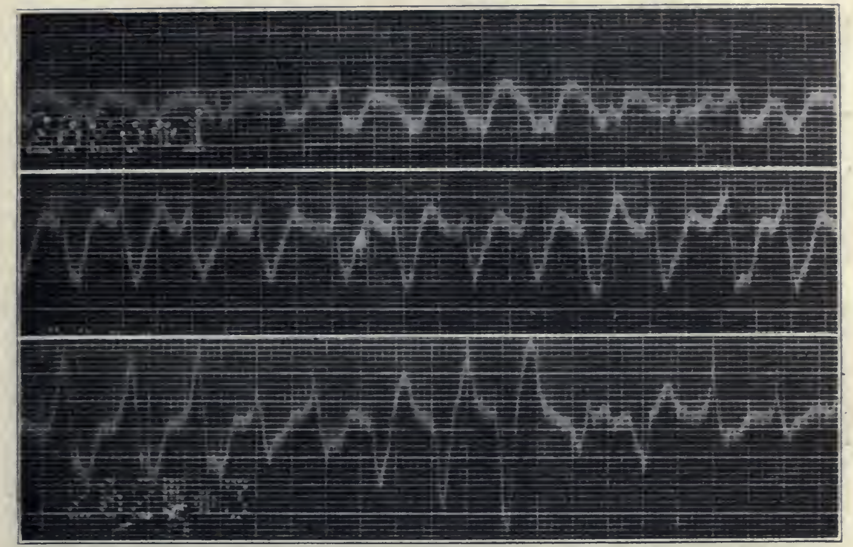

Figure 2

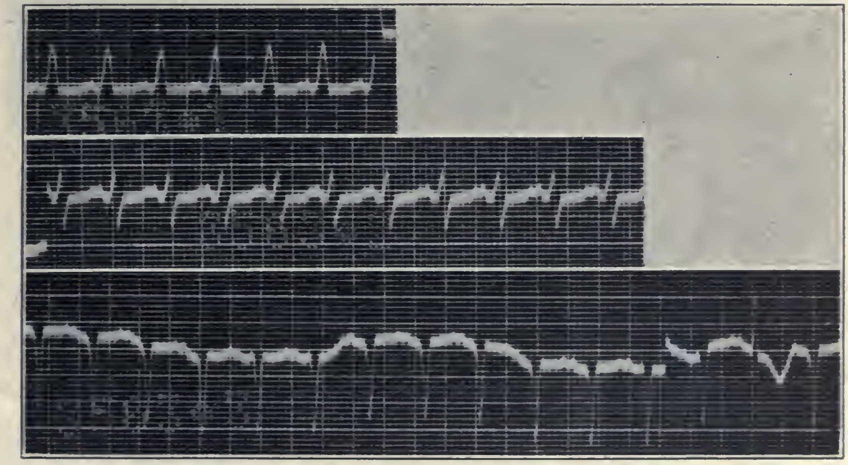

Figure 3

Electrocardiogram [No. 2657] (Fig. 4).—This record was made June 28, and shows a block of the impulse in the right branch of the bundle of His. The Q R S time is 0.100 second, a slight delay; the complexes are not otherwise abnormal. The S T time is 0.280 second, not delayed. The T wave is inverted in Lead I and Lead II, but is upright in Lead III. The ventricular rate is 126.3 per minute, the P R time 0.120 second.

Interpretation: There is heart block in the right branch of the bundle of His.

Electrocardiogram [No. 2659] (Fig. 5).—This was made June 29, and shows the Q R S time to be 0.100 second; the complex is abnormal in all three leads, suggesting a disturbance of the impulse conduction in the right branch of the bundle of His. The complex is quite different from that seen in Figure 4. The S T time is 0.320 second, the T wave is inverted in Lead I, but is upright in Leads II and III. The ventricular rate is 104.3 per minute; the P R time is 0.140 second.

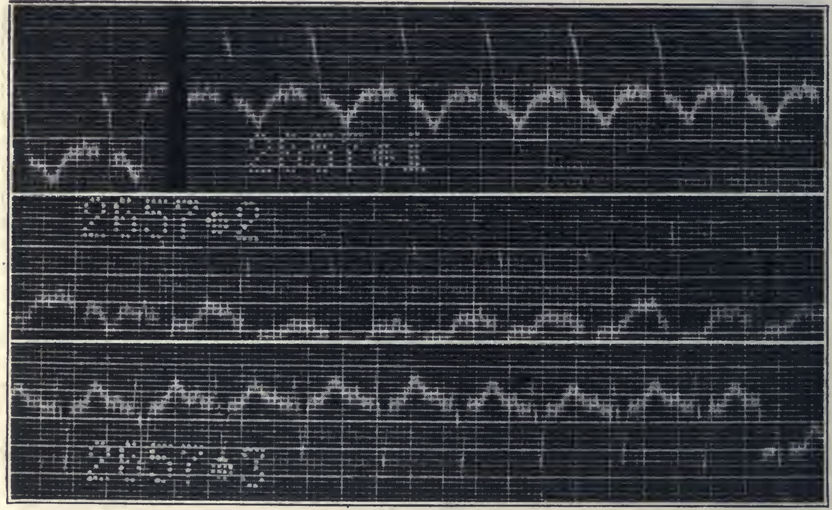

Figure 4

Interpretation: There is a disturbance in conduction in the right branch of the bundle of His. This curve, as compared with Figure 4, shows some improvement in the cardiac condition.

July 6, it was noted that the heart had dilated to 1 cm. outside the nipple line. There was a paralysis of the soft palate, which condition grew rapidly worse. Signs indicating heart failure were present, manifested by dilatation, tachycardia and distress. The point of maximum impulse was weak and diffuse; there were no murmurs. The pulse was weak and at times irregular. The patient was slightly cyanotic.

Electrocardiogram [No. 2663] (Fig. 6).—This tracing was made July 11, and shows an inverted P wave in Leads II and III. The Q R S time is 0.060 second; the complexes are low in amplitude but otherwise the form is normal. There is evidence of disturbance in intraventricular conduction, a very marked change from Figures 4 and 5. The T wave is upright in Leads I and II but is inverted in Lead III. The ventricular rate is 126.3 per minute; the P R time 0.160 second.

Interpretation: Except for the inversion of the P waves in Leads II and III, the curves are normal.

The patient continued to fail, the heart becoming more and more irregular, the irregularity being caused by many ectopic contractions. The pulse was very weak. The patient died twelve hours after the last electrocardiogram was made. At necropsy the heart weighed 85 gms. The cut edge of the heart wall was yellowish in color. No defects were seen on the valves. The remainder of the gross examination was unimportant.

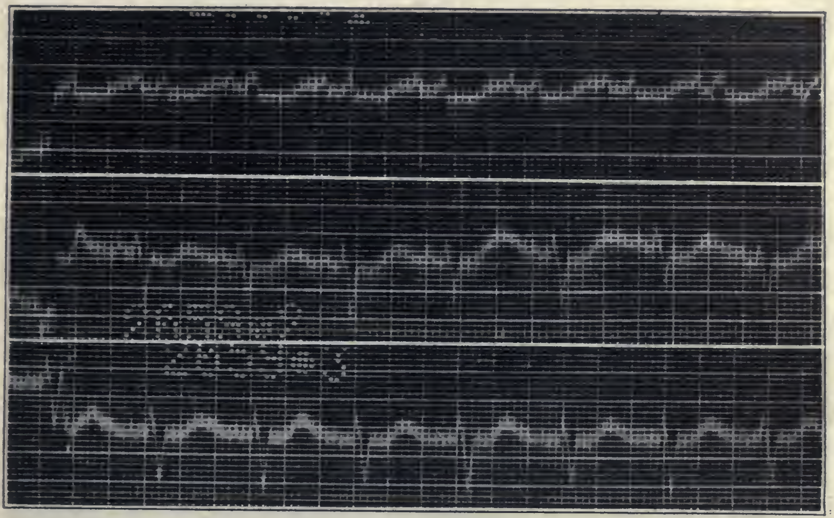

Figure 5

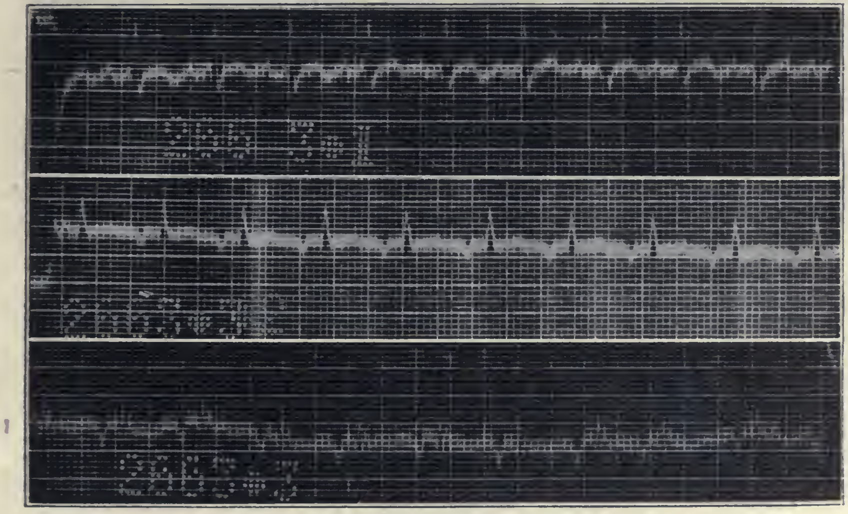

Figure 6

Case 4 (Children's Hospital No. 13567.—This patient, aged 5 years, was admitted Dec. 14, 1918, with the history of an onset of pharyngeal diphtheria, December 11. Antitoxin, 10,000 units, was administered on admission. The heart was normal and not enlarged, with normal rhythm. There was an uneventful convalescence with no unfavorable signs until Jan. 3, 1919. At this time the patient was suddenly attacked by a pain in the abdomen, with distress and dyspnea of such a nature that the picture simulated an acute surgical condition of the abdomen rather than a cardiac failure. On examination, twelve hours after the onset of the acute pain, the heart was beating very forcibly and was very rapid but regular; the rate was 220 per minute; there were no murmurs. The heart was greatly enlarged, especially to the left. The sounds were weak; the pulse was almost imperceptible and could not be counted. The liver was enormously enlarged. There were slight cyanosis and slight dyspnea. The face was pale and swollen. Vagus pressure produced no effect on the pulse rate.

Electrocardiogram [No. 2136] (Fig. 7).—This record, made Jan. 4, 1919, indicates widespread disturbance of the cardiac mechanism, the conduction and impulse formation of both auricles and ventricles being affected, probably by a myocardial lesion. There are abnormal ventricular complexes, not typical of bundle branch block, nor of predominance of one ventricular muscle mass over the other. There is an auricular arrhythmia caused apparently by the frequent occurrence of ectopic premature auricular beats, occurring singly or in groups. In some parts of the record, the point in the auricles which is the site of the ectopic beat formation becomes the pacemaker, and the rate of the heart is changed. The rate, when the normal pacemaker is in control, is about 117 per minute, while it increases to about 153 when the ectopic center becomes the pacemaker. The P waves of the ectopic beats are poorly defined and the auriculoventricular interval following them cannot be measured definitely. There is a block of some of the auricular impulses, and this seems to occur only with the ectopic premature contractions.

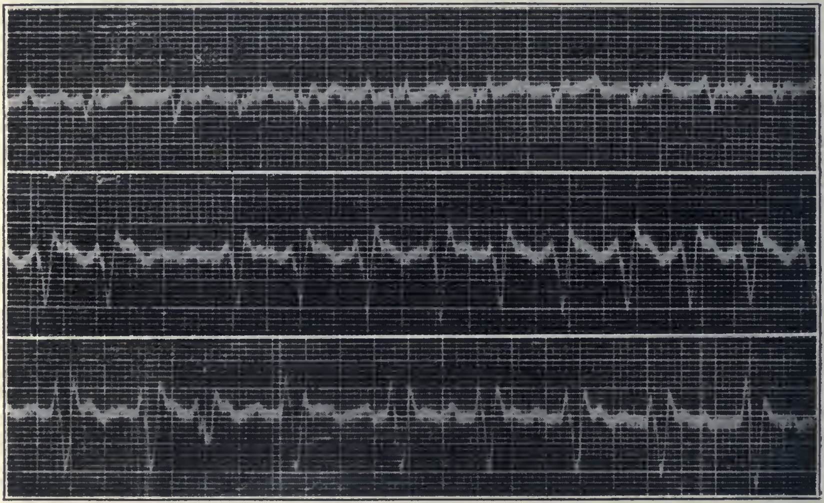

Figure 7

Conduction from auricles to ventricles is usually about 0.200 second, but it varies somewhat, even when the impulses seem to arise in the normal pacemaker. The form of the ventricular complexes changes somewhat and an occasional ectopic ventricular contraction occurs. The intraventricular conduction is disturbed as well, the Q R S time being about 0.180 second.

The next day there was a marked change in the findings, the heart being much reduced in size, 8 cm. to the left, almost to normal. The liver was much smaller. There was gallop rhythm but no murmurs. Reduplication of one sound was detected at the apex but it was impossible to say which sound. The patient was much better.

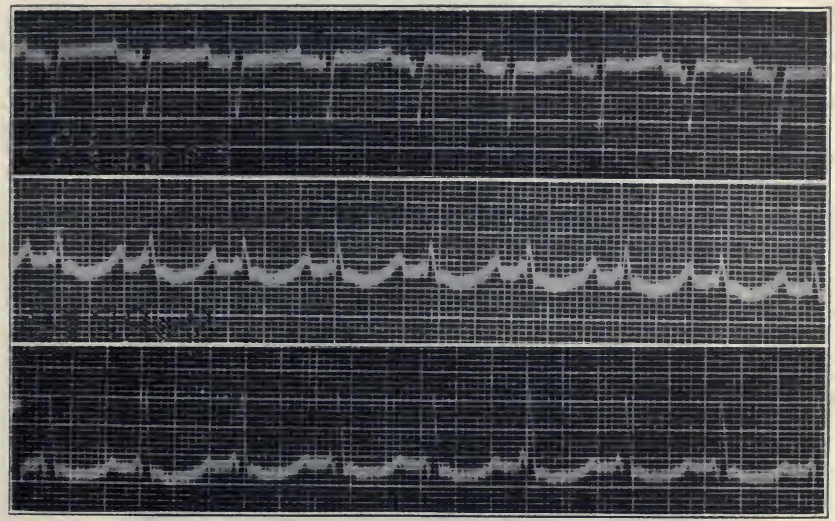

Figure 8

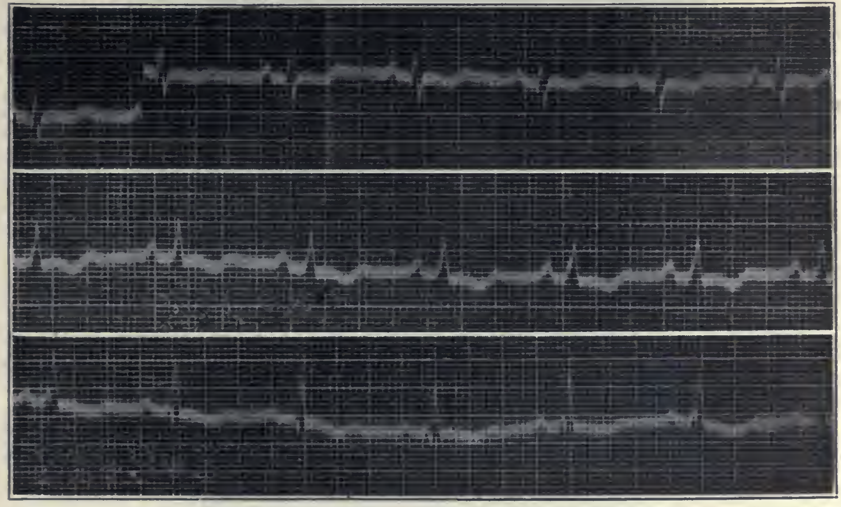

Figure 9

Electrocardiogram [No. 2139] (Fig. 8).—This record, made Jan. 5, 1919, 10 a. m., shows a striking change in the form of the ventricular complexes. The complex now suggests increased preponderance of activity on the right side. It is possible that the form of the Q R S group, together with the alteration of the form of the T wave, may be due to disturbance in conduction.

The S T time is difficult to measure, but there does not seem to be a delay. However, the Q R S time is 0.100-0.120 second, which is not much of a delay. The T wave is iso-electric in Lead I, but is inverted in Leads II and III. The ventricular rate is 110.0 per minute; the P R time is 0.160 second.

Interpretation: There is right ventricular preponderance, and possibly some disturbance in intraventricular conduction on the left side.

Jan. 10, 1919, the heart was normal in size; the rate was 80. The liver was normal size. The splenic enlargement and tenderness had disappeared, and the general appearance was normal.

Electrocardiogram [No. 2149] (Fig. 9).—This tracing, made January 9, shows normal cardiac mechanism. The notching of the R wave, noted in Figure 8, has disappeared entirely. The Q R S complex time is 0.090 second and the complex is suggestive only of a slight right ventricular preponderance. The S T time is 0.240 second. The T wave is inverted in all leads. The ventricular rate is 104.3 per minute; the P R time 0.160 second.

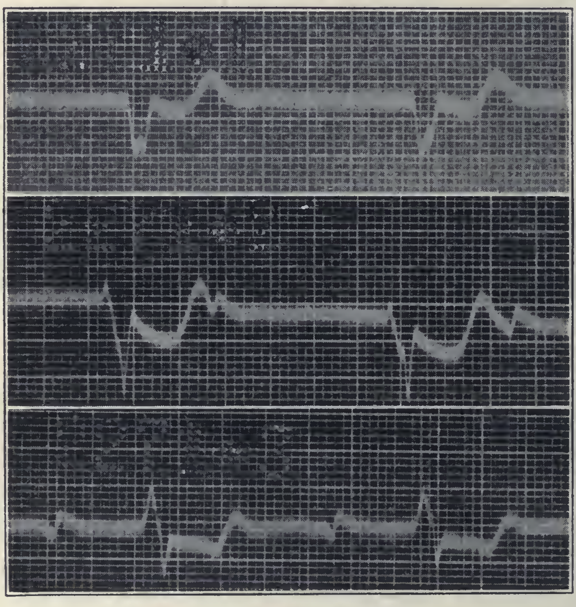

Figure 10

Interpretation: There is possibly a slight right ventricular preponderance; otherwise the curves are normal.

January 13, the patient was discharged from the hospital on the wishes of the parents and against our advice. Three weeks later word was received that the patient had died suddenly, following only slight exertion. The nature of the death was not ascertained. No necropsy was allowed.

Case 5. (Children's Hospital No. 13762).—This girl, aged 8 years, was admitted Feb. 9, 1919, with a history of onset of pharyngeal diphtheria three days before. After admission she was given 12,000 units of antitoxin. The heart was normal, and without enlargement. The heart rate was slow, between 80 and 90, but regular.

Electrocardiogram [No. 2271] (Fig. 10).—This was made Feb. 14, 1919, and shows complete auriculoventricular heart block. The auricular rate is

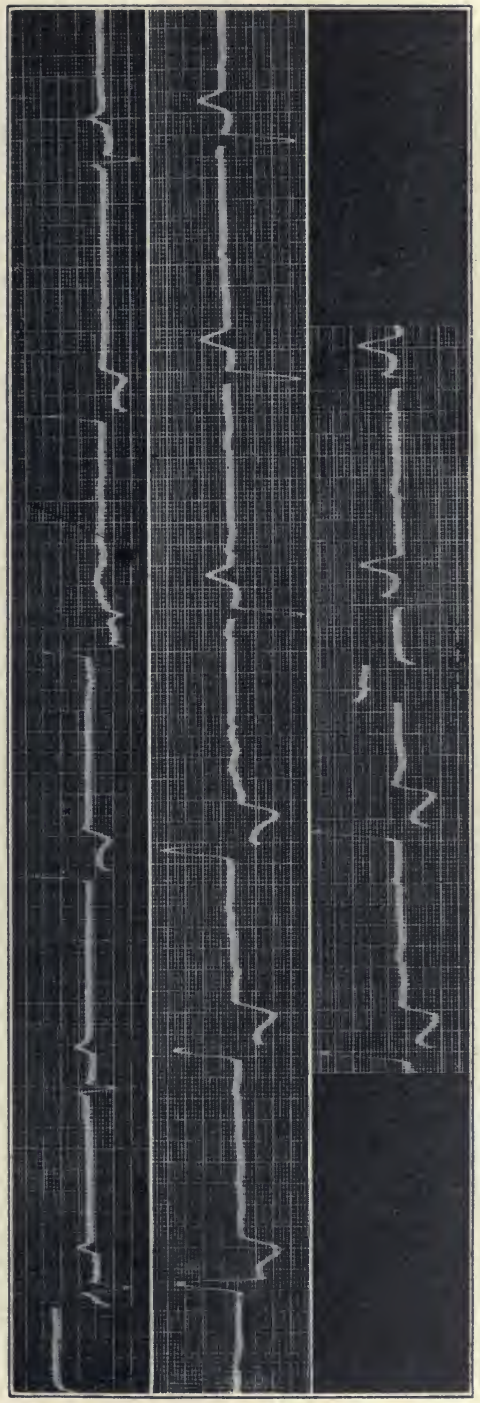

Figure 11

40.0 per minute; the ventricular rate is 49.0. There is also marked disturbance of conduction of the impulse through the ventricles. The Q R S complex is abnormal in form in all leads. The S T time is 0.400 second, a moderate delay. The T wave is diphasic, the initial part of the phase being directed downward.

Interpretation: There is complete auriculoventricular heart block with marked disturbance in intraventricular conduction.

February 14, she was vomiting everything taken by mouth. The cardiac outline was not changed; the first sound was slightly impure at the apex. Slight cyanosis was observed. The liver was not palpable.

Electrocardiogram [No. 2275] (Fig. 11).—This record was made February 15, and shows complete auriculoventricular heart block. However, in the curves, the focus controlling the ventricular impulse and rate, instead of being located in the conducting tissue of the bundle below the block, as in Figure 10, is located at some point outside the bundle, either in the bundle branches or in the ventricles themselves. The complexes resemble right or left bundle branch block, or premature contractions arising at one time in the right ventricle, at another within the left ventricle. These foci of origin produce complexes that are decidedly abnormal as compared with the normal and with Figure 10. There are no normal ventricular complexes in this record, nor are there any periods when the complexes show well marked transition forms. The change in each instance from right to left ventricular control, or vice versa, is abrupt. At no time would it seem that two stimuli, arising simultaneously in the two branches, have coincided to produce a normal complex or a complex resembling those in Figure 10.

The child died twelve hours after this record was obtained. No necropsy was allowed.

Case 6 (Children's Hospital No. 12587).—A girl, aged 12 years,[7] was admitted to the hospital March 25, 1918, with pharyngeal diphtheria, the onset of which occurred March 15. March 17 5,000 units of antitoxin were given, and three days after that the child was apparently well. She was admitted to the hospital because she had become worse and complained of pain in her heart. Her heart was beating at a rate of only 40. The point of maximum impulse was 1 cm. outside the nipple line, but the sounds were clear. She was in a semiconscious condition.

Electrocardiogram [No. 1547] (Fig. 12).—This record was made March 25, 1918, and shows complete auriculoventricular heart block. The auricular rate is 78.8 per minute; the ventricular rate is 35.8. The Q R S time is very much delayed, amounting to 0.240 second; the complexes are very abnormal in form and suggest a marked disturbance in intraventricular conduction. The S T time is difficult to measure.

Interpretation: There is complete auriculoventricular heart block and possibly some disturbance in intraventricular conduction.

March 27, it was noted that the heart apex could not be seen nor felt. There was dulness 9 cm. to the left of the median line. There were murmurs but the sounds were blurred; the rate was 34. No evidence of cardiac insufficiency was present.

Electrocardiogram [No. 1549] (Fig. 13).—In this record, made March 27, only the second lead is shown. This shows complete auriculoventricular heart block. The auricular rate is 83.3 per minute; the ventricular rate 36. The first three complexes in the record resemble those due to block in the right bundle branch, and the last two complexes are due to left bundle branch block. The fourth and fifth complexes are transition complexes. The area of disturbance in the bundle causing the block has now extended down to a

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[7] Robinson, G. C.: Washington Univ. Bull. Med. School, Third Series, Sept. 1918.

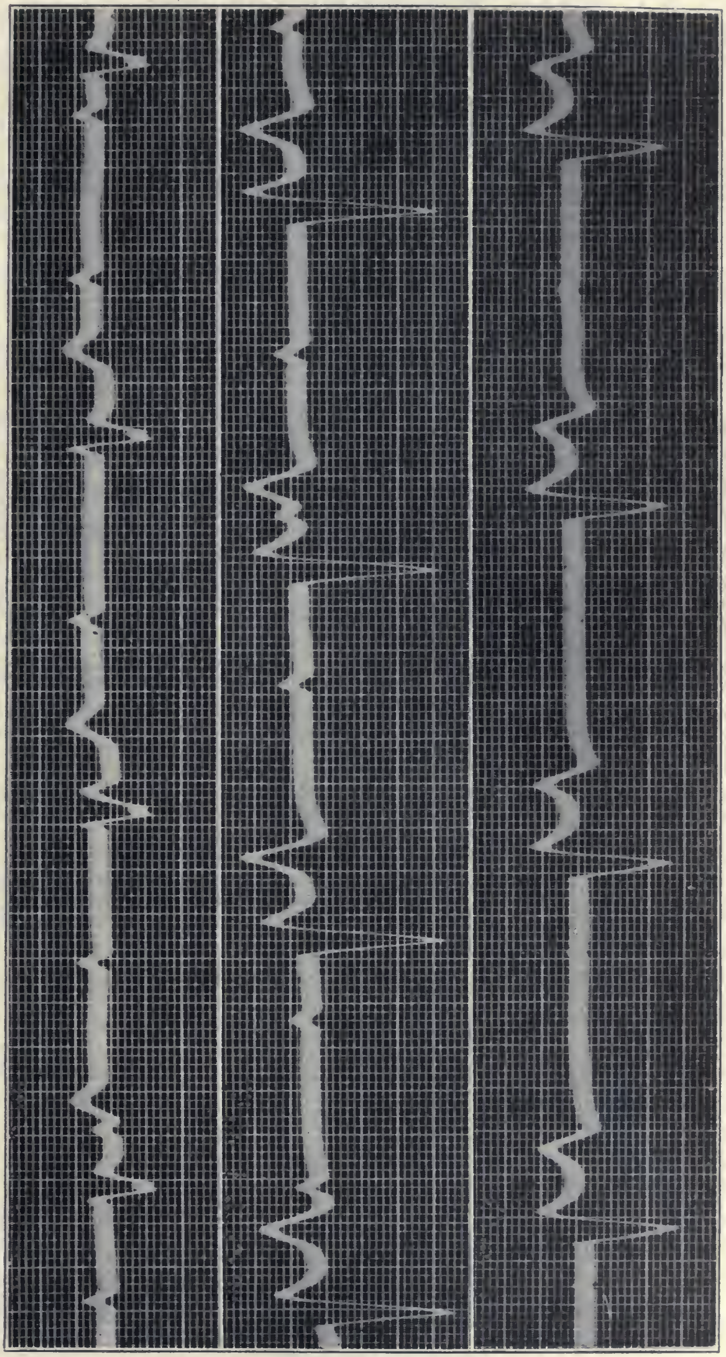

Figure 12

point below the branching of the bundle, and the impulses controlling the ventricular rate are arising in the conducting tissue, first in the left branch, then in both branches simultaneously, and finally in the right branch.

The child showed no signs of improvement and died March 28. No necropsy was allowed.

Case 7 (Children's Hospital No. 15043).—An infant, aged 12 months, was admitted Jan. 19, 1920, with the information that she had been sick for three or four days. There were short respirations, cough and vomiting. Pharyngeal diphtheria was diagnosed. The heart was not enlarged, and no murmurs were detected. On the following day she received 7,500 units of antitoxin. The fever declined to normal. The pulse rate was normal.

Electrocardiogram [No. 3423].—This record, made Jan. 19, 1920, shows normal cardiac mechanism, with a slight physiological right ventricular preponderance. The Q R S time is 0.060 second and of normal form. The S T time is 0.200 second, and the T waves are upright. The ventricular rate was 166.7 per minute; the P R time 0.120 second.

Interpretation: Normal curves.

January 22, the child began to have bleeding from the nose, most of the blood being swallowed. She would not take her food.

January 23, she was still vomiting, chiefly it was thought, from an acidosis. She was cyanotic and her heart was regular. However, at 10 p. m., she showed signs of heart failure. The pulse was weak; the heart was enlarged 0.5 cm. beyond the left nipple line, but was not enlarged to the right. The heart sounds slow and irregular, were largely obscured by the breathing.

Electrocardiogram [No. 3458] (Figs. 14, 15 and 16).—This record, made January 24, shows complete auriculoventricular heart block. The auricular rate is 60.0 per minute. The ventricular rate is 66.7. The Q R S complexes are all abnormal in form and indicate marked disturbance of conduction in the ventricles. During certain periods the complexes have the form of block in the right branch of the bundle of His. No normal complexes are to be seen.

January 24, several hours after these curves were made, she died.

At necropsy, the heart was found to weigh 50 gm.; the valves were normal. The myocardium, especially that of the right ventricle, was mottled by light yellowish areas giving a typical "thrush breast" appearance.

Figs. 14, 15 and 16.—(Electrocardiogram [No. 3458].) In Figure 14 the first and second curves are a continuous record of Lead I. The lead was changed quickly and the third curve was made, being Lead II. Again the lead was changed quickly to Lead III and curves 1, 2, 3, 4, 5, 6 and 7 in Figures 15 and 16 were obtained. This is a continuous record, reading from above downward and from left to right. This lead was observed for several minutes more to see if there was any return of the transition complexes. There being none, the lead was changed again to Lead II, the curve of which is shown in Figure 14, curve 4. The patient's heart was under direct observation by watching the galvanometer at frequent intervals for the next two hours, but no further transition complexes were observed.

DISCUSSION

Cases 1 and 2 are representative of twelve cases in which the conducting tissue in the heart showed no evidence of injury, although there were disturbances and lesions in the heart muscle. In the cases of this group, the hearts were enlarged both to the right and to the left. There was a weak diffuse impulse over the precordium; the sounds were weak, blurred and at times there were transitory mur-

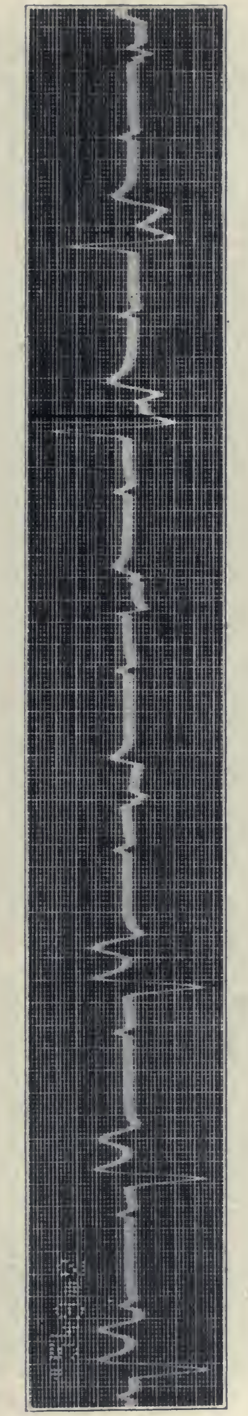

Figure 13

murs, systolic in time; the heart rate was very rapid and gallop rhythm was frequently noticed. The electrocardiograms in these cases have shown no gross abnormality. There is usually evidence of preponderance on the right or the left side of the heart. Most frequently this is on the left side, the result most probably, of failure of the right ventricle. The most frequent disturbance observed in the electrocardiogram in this type of case is some disturbance in intraventricular conduction. The Q R S time is prolonged, the amplitude of the R wave is much diminished and the T wave becomes inverted, often in all three leads. These changes were observed in both of the cases reported. The delay in conduction in the ventricles may be due to disturbance in the conducting tissue, although I am of the opinion that it is more readily explained by the increase in size of the dilated and hypertrophied ventricle, necessitating a longer time for the impulse to reach the ventricle and cause it to respond. In our cases in which the diagnosis of myocarditis had been made, there has always been some change in the electrocardiogram, such as has been described. These changes are all transitory, and if the myocarditis is not fatal they tend to disappear during recovery.

Signs of heart failure made their appearance in this group during convalescence, when, with more exertion or undue exercise, the cardiac reserve, sufficient for rest, was not able to met the demands for work put on it. In four of this group of twelve cases, the damage to the heart was so great that all cardiac reserve was used up, even with complete rest, and death resulted, yielding a mortality rate of 33 per cent. The other eight patients after a stormy period in which the cardiac failure was more or less severe, began to improve and gradually recovered sufficiently to allow their discharge from the hospital. Their convalescence extended over three weeks. On subsequent examinations, some as long as a year after the cardiac failure, these patients are doing well and show no evidence of any disturbance.

In this study several cases occurred, two of which are described (Cases 3 and 4), in which there was extensive damage to the muscle with disturbance in the cardiac mechanism as well. Both patients showed evidence of acute myocarditis with cardiac failure during the course of diphtheria. In case 3, (No. 2657, Figure 4) there was cardiac failure with evidence in the electrocardiogram of delayed conduction, probably a block in the branch of the bundle of His. This disturbance, as observed in subsequent records (No. 2659, Fig. 5, and No. 2663, Fig. 6), seemed to be improving, the last record being within the limits of normal. In Case 4, (No. 2136, Fig. 7) there were grave disturbances in the cardiac mechanism, both the heart muscle and the impulse conducting system being affected. Clinically, there was car-

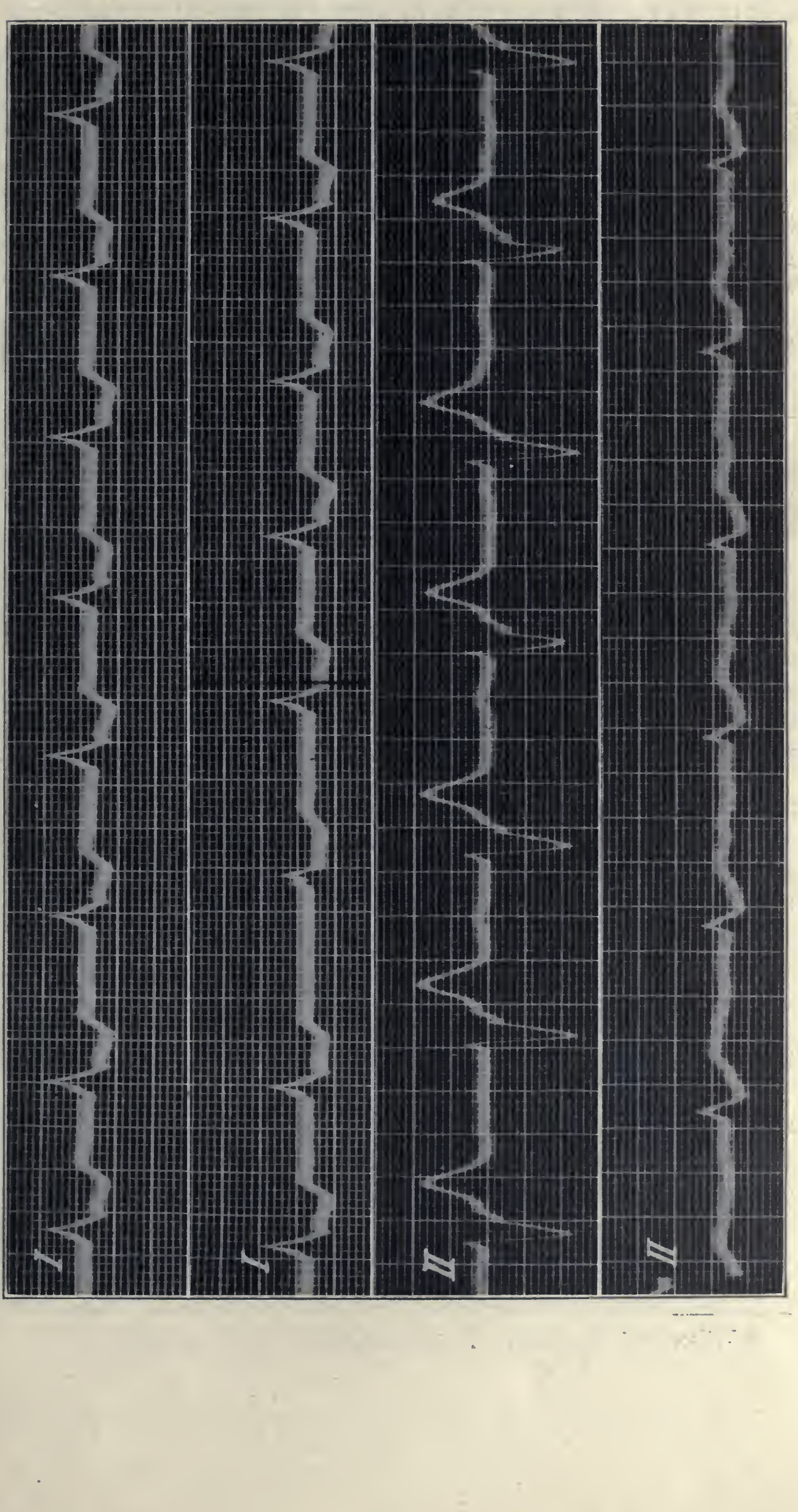

Figure 14

diac failure and the record (Fig. 7) showed that stimuli were arising at points in the auricle other than in the sino-auricular node, and that these abnormal foci at times became pacemakers for the auricles. Further, the record showed disturbances in conduction, both delay and, at times, block of the impulses passing from auricles to ventricles. This case, too, showed signs of improvement both clinically and in the electrocardiogram. In Case 3, death resulted because there was increasing failure of the heart muscle until the reserve power was gone. The nature of death in Case 4 is doubtful, but it may be assumed that the cardiac reserve was used up following exertion. These cases represent mild or moderate effects on the cardiac mechanism that may or may not be fatal. The disturbance occurred in this type of case during the acute stage or early in the convalescence from the disease.

Three cases (Cases 5, 6 and 7) serve as illustrations of profound effects on diphtheria on both the heart muscle and the cardiac mechanism, particularly the latter. These disturbances have occurred in our cases during the acute stage of the disease before convalescence was well established. They have invariably been fatal, the child living only a few days after the onset of the disturbance. In Case 6, the initial sign was a slow pulse of 40, appearing before it was recognized that a myocarditis existed. The disturbance in mechanism dominated the clinical picture in all three of these cases. There were widespread disturbances causing complete auriculoventricular dissociation with abnormal foci controlling the ventricular rate.

In Case 5 (No. 2275, Fig. 11) and in Case 6 (No. 1549, Fig. 13), it is probable that all the conducting tissue in the bundle and down to a point below the branching of the bundle was affected. In such a case the pacemaker controlling the ventricles was located in the branches below the block. In long strips of the records it may be seen that this is located first on the left side, then on the right side, and varies in position, being first in one and then in the other. If the impulse arises in the left branch, it produces complexes similar to those seen in right bundle branch block; if it arises in the right branch, it produces complexes similar to those seen in left bundle branch block. The impulse arising in one branch passes down to the ventricle on the same side and through the septal tissues to the conducting tissue in the ventricle on the opposite side. It is impossible to gain entrance to the opposite side without first going through the same side. This explanation of the location of impulse formation and path of conduction of the impulses is supported by animal experiments done by Wilson and Hermann,[8] working in this laboratory.

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[8] Wilson and Herrmann: To be published in Arch. Int. Med.

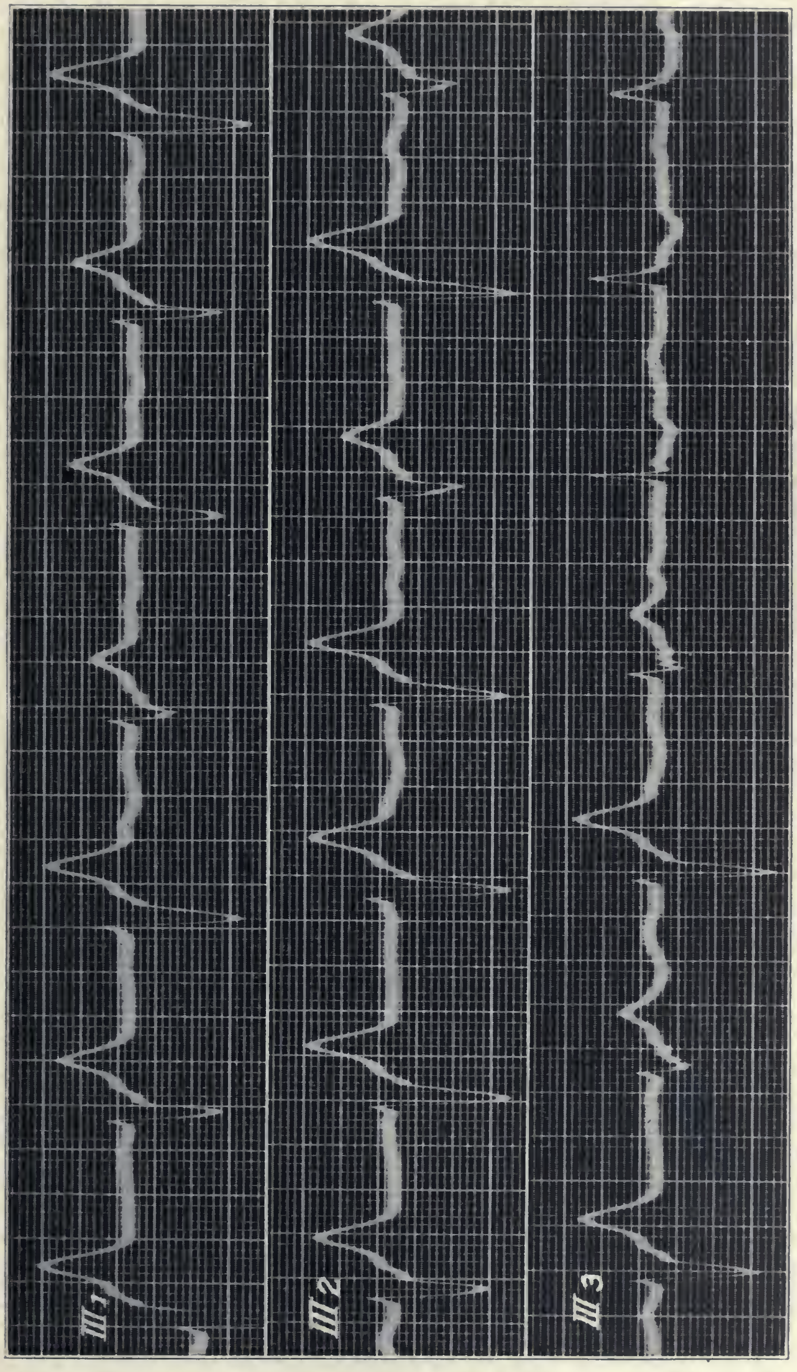

Figure 15

Another possible explanation of the phenomena in these records is that with a complete destruction of all the conducting tissue, not only in the bundle but also in the branches, the stimulus is no longer able to arise in or to spread through the branch. The rôle of pacemaker under these circumstances is assumed by ectopic foci located in the ventricular muscle, first in the left and next in the right ventricle, and varying first in one position and then in the other. The time in the cardiac cycle at which the various foci send out their impulses determines which stimulus shall produce the ventricular response in that cycle. The ventricle continues under the control of that focus for a time, when the control or rate is assumed by another focus. Stimuli arising simultaneously may produce a summation of their effects, with a resulting complex either normal or similar to those that existed before the disturbance occurred. However, ectopic foci outside the conducting tissue are apparently never able to control the ventricles at such a slow rate as shown in these curves. Ectopic foci in the ventricles produce either single premature contractions or ventricular tachycardia or fibrillation, both of which show rapid ventricular rate. Furthermore, if the stimuli arise in the ectopic foci in the ventricles, outside the conducting tissue, they will do so only if the conducting tissue is entirely destroyed. For ordinarily the function of the conducting tissue is such that it assumes the rôle of pacemaker more readily than foci in the muscle. The form of the ventricular complexes resembles both ectopic ventricular contractions and complexes due to bundle branch block.

Case 7 (No. 3458, Fig. 15) shows complete auriculoventricular dissociation with abnormal ventricular complexes indicating marked disturbance in intraventricular conduction. The impulse causing the ventricular contraction arises in the bundle of His below the area of disturbance that causes the auriculoventricular block. Furthermore, there are periods in which the complexes have the form of right bundle branch block. During these periods the impulse, originating in the bundle and encountering the disturbance in the right branch, passes down the left branch and to the right ventricle through the septal tissues. At no time is there any evidence of block in the left branch. In this record (Figs. 15 and 16), Lead III shows many complexes that represent transition forms, similar to those in Case 5 (No. 1549, Fig. 13), though in this record (Fig. 15) the transition is more gradual and does not show a transition to the left bundle branch block. In the beginning of this lead, there is a block in the right branch. This block is not permanent and is removed gradually so that irregularly at first, and then constantly, the impulses pass down that branch as well as the left. In Lead III the third, eleventh, thirteenth,

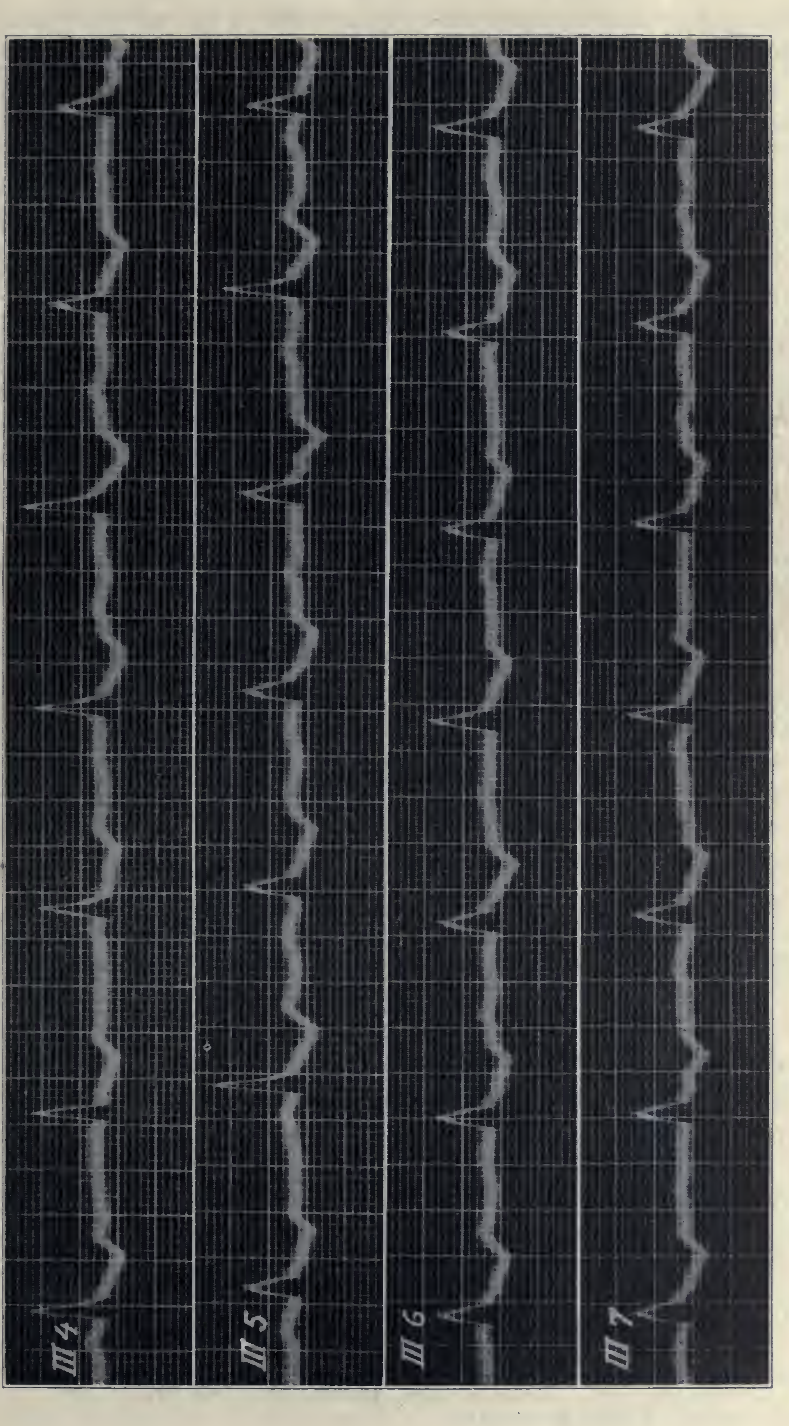

Figure 16

fifteenth, seventeenth, eighteenth and nineteenth cycles represent transitional ventricular complexes in which the impulse is beginning to have passage through the right branch. By the time the twentieth cycle is reached, the period of transition may be said to be completed.

In the cases in this group, we have evidence that abnormal complexes may arise in the ventricles and that the form of the complex may vary in many ways in a short interval of time. These phenomena probably are due to functional rather than anatomic changes in the tissues.[9]

Sudden death is not uncommon, and is due to the disturbances in the heart, most often in the conducting system, or to changes in the respiratory center, and not to associated degeneration in the vagus or sympathetic nerves. In the study of our cases, we have noted frequently signs of general vasomotor disturbances with failure, such as Gunson mentions,[10] but these cases have shown as well profound disturbances in the heart, as revealed by the electrocardiogram. The changes in the heart and the paralysis seen from degeneration of the nerves, particularly the vagus, though dependent on the same cause, are actually independent of each other. Cardiac disturbances as a consequence of vagus lesions in diphtheria are uncommon. As a result of the local action of the toxin on the nerve, there may be vagus stimulation and slowing of the pulse rate. In cases that we have studied, there has been no evidence found to show that there was stimulation of destruction of the vagus fibers to the heart. It could be shown that pressure and stimulation of the vagus were effectual in slowing the heart. Release the heart from vagus control by the use of atropin showed a further increase in rate.

In the observation of these cases, it has not been possible to say with certainty what factor has been responsible for the occurrence of the heart failure. The failure is more prone to occur in cases that for one reason or another have received antitoxin late in the course of the disease, allowing a greater interval of time for the toxin to act on the tissues before they are neutralized by the antibodies furnished actively by the patient's own response to the infection, or passively by the therapeutic administration of antitoxin. In some cases, the antitoxin has been given, but in insufficient quantity, or it was injected subcutaneously rather than intramuscularly or intravenously. In some cases the symptoms occur in spite of the early recognition and specific treatment. There is no relation between the heart symptoms and the location of the local inflammation or the extent of the membrane in that location. Cases that impress one as being more toxic are prone to show these signs, and yet these may occur when the attack has seemed to be mild.

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[9] Robinson, G. C.: Arch. Int. Med. **18**:830, 1916; ibid. **24**:422, 1919.

[10] Gunson: Lancet **2**:670, 1917.

We have come to know that scarlet fever, tonsillitis and other infections play an important part in the production of infectious lesions in the heart, resulting in pericarditis, myocardtis and endocarditis. Diphtheria occupies an analogous position in the production of myocardial lesions. The initial lesion is an acute myocarditis resulting from the action of the diphtheria toxin. The attempts at repair produce a chronic fibrous myocarditis, which ultimately comes to show the same signs as chronic myocarditis resulting from other causes.

The cases described represent well marked examples of effects of diphtheria on the heart and the structures controlling its mechanism, rate and efficiency as an organ of work. There were sixty-one cases, 85 per cent. of the whole group, in which it was not possible to recognize such lesions.

However, many of these so-called latent myocardial lesions may become apparent at some future date. This may not be until puberty or even until later when the individual undertakes severe exercise and manual labor or in the mental stress of adult life. The failure may be postponed until the period is reached when there is deterioration of the whole organism. And in such cases, diphtheria as an etiologic factor in the production of the heart failure is often lost sight of.

CONCLUSIONS

1. Nineteen cases of diphtheria from a group of eighty showed evidence of cardiac disturbance.

2. In those cases in which the effect on the heart is so profound as to interfere with the cardiac mechanism, the outcome is usually fatal. In this study the mortality rate was 100 per cent.

Patients whose heart muscle alone is involved depend for their recovery largely on the ability to preserve a cardiac reserve sufficient for their needs. The moment this reserve is used up, cardiac failure results.

3. In these cases we find further evidence that severe functional changes occur, causing disturbances in the cardiac mechanism.

4. The occurrence of myocarditis following diphtheria is largely beyond our control; although the outcome is determined at least in some cases, by the protection the heart receives during the course of the disease and during convalescence.

5. Myocarditis due to diphtheria has a definite position among those factors that lead to chronic heart disease later in life.

DISCUSSION

Dr. Richard S. Eustis, Boston: Dr. McCulloch is to be congratulated on showing so well the effects of diphtheria toxin on the heart muscle. He has emphasized the important point, which is the effect on the heart muscle rather than on the heart valves. He has brought out precisely what happens, and has shown that it is the diminution of the cardiac reserve which cause the fatal ending in so many of these cases. I feel that the application of the electrocardiograph will show a great deal more in the future in connection with heart disease, due to other causes. We already find partial heart block, or delay in the conduction time, in some of the earlier rheumatic cases, and probably further observation will enable us to state whether or not the cardiac reserve is being encroached on seriously.

Dr. Fritz Talbot, Boston: Like all new work, Dr. McCulloch's work is very important. When any new method comes into use, it takes many of us some time before we can understand the technicalities which must necessarily be mastered before we can make use of it. There is no doubt, however, that by the use of the electrocardiogram we are receiving much new knowledge, which is of the greatest value in the treatment and recognition of the condition with which we are dealing.

A NEW METHOD OF DIAGNOSIS OF PERITONITIS IN INFANCY AND CHILDHOOD

PRELIMINARY REPORT *

BERNARD DENZER, M.D.
NEW YORK

It is generally recognized that the diagnosis of peritonitis in childhood and particularly in infancy presents a difficult problem. Peritonitis is frequently found at necropsy, when it had not been suspected during life, and, on the other hand, it is often impossible to exclude peritonitis as the cause of obscure febrile conditions in infancy.

Our purpose was to obtain a specimen of peritoneal fluid in order to determine the initial reaction to the inflammatory process. Aspiration has several disadvantages. First, a comparatively large amount of fluid must be drawn through the metal needle and into the barrel of the syringe before one can observe whether fluid has been obtained. Second, aspiration is apt to suck omentum or intestine to the needle point, damage the intestine, or, at least, block the needle and thus prevent the aspiration of fluid even though it may be present. Furthermore, we believe that aspiration has been attempted, and that it has been discarded or at least has not proved of sufficient value to warrant further trial.

The classical Pfeiffer experiment, in which a capillary tube is inserted into the peritoneal cavity of a guinea-pig and fluid obtained by capillary attraction, suggested the procedure we finally adopted. Glass needles have been used. They were prepared from glass tubing 3⁄16 inch thick with a bore of about 1⁄32 inch, and were drawn to a point and beveled. In order to add siphonage to the force of capillary attraction and obtain a larger amount of fluid, a bulb was blown and the tubing bent.

METHOD OF PROCEDURE

The procedure is as follows: the skin of the abdomen is swabbed with iodin and the usual precautions are taken to determine bladder distention. A steel needle, about number 17 gage, is used to puncture the skin in the midline about one-half inch below the umbilicus. The glass needle is inserted through this opening and then, held almost perpendicular to the surface of the skin, it is firmly pushed inward until the sudden release of pressure indicates that the needle has

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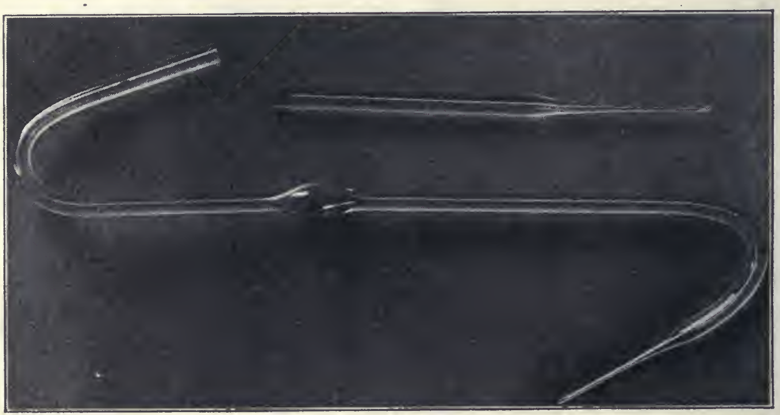
* From The New York Nursery and Child's Hospital and The Pediatric Department, Cornell University Medical College.

entered the peritoneal cavity. By making the pressure parallel to the long axis of the needle the likelihood of breaking the needle is decreased.

In a small series of normal children, or, rather, children not suffering from peritoneal exudation, fluid was obtained in only one case. The amount was sufficient only for a few smear preparations. In two cases of ascites, before a clinical diagnosis of excessive fluid could be established, puncture demonstrated the presence of fluid. In one case 0.5 c.c. was obtained. In the only case of peritonitis in which we have had the opportunity of trying this procedure, purulent fluid was obtained. The amount was ample for culture; smears showed great numbers of gram-positive cocci in chains. This experience, brief as it is, establishes abdominal puncture with a capillary tube as a possible method for the diagnosis of intra-abdominal exudates.



The upper figure shows the straight capillary needle. The lower figure is that of the needle used when siphonage is desired.

Glass needles have distinct advantages. The capillary attraction of glass is far greater than that of metals, and the smallest amount of fluid rising in the tube can readily be seen. The one disadvantage is fragility. We are at present experimenting with needles and trocars of metal and glass in the hope of combining the advantages of both materials. These and further studies on peritoneal fluid will be the subject of a later communication.

A TWENTY-FOUR HOUR SCHEDULE FOR SCHOOL BOYS *

RICHARD M. SMITH, M.D.
BOSTON

In a previous communication [1] I drew attention to certain fundamental principles with reference to the care of the health of school children, and pointed out lines for further extension of health supervision. It was stated that "there must be a general recognition of the importance of health and a realization among the school authorities that the health of children is as important as scholarship," and that there was "special need in securing the cooperation of parents in protecting the health of their children." I also presented a table of the distribution of the boy's time during school hours between study, activity and inactivity. I am convinced by a further use of the table that it gives a correct distribution of the boy's school time. It became obvious, however, in the application of this table to the individual child, that no satisfactory plan for the boy could be made without a coordination of the school schedule with the time that the boy spent away from school.

The child may be considered as the center of a triangle, the base of which is represented by the home and the two sides by health and education. The parent, the physician and the teacher are together responsible for the child's life, and no part of that life can be arranged intelligently without the cooperation of all three individuals. For instance, the child's physical environment, such as buildings and fresh air, is dependent not alone on the proper sanitation of the school building, but on the room in which he sleeps at home. His nutrition is maintained not only by the school lunch and the dinner received at school, but also by the breakfast and the supper given at home. His educational work in school must be arranged, bearing in mind not only the studies necessary for the school curriculum, but also whether or not he is doing work at home, such as studying music and languages. His exercise is made up of what he does at home in the afternoon quite as much as of the carefully arranged athletics at school. His periods of relaxation at school and at home together make up the relatively inactive portion of his day.

During the last year, at Mr. Rivers' Open-Air School for Boys, we made a study of the weekly twenty-four hour distribution of the

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* Read at the Annual Meeting of the American Pediatric Society, held at Highland Park, Ill., May 31 to June 2, 1920.

[1] A Health Study of a Boys' School, Am. J. Dis. Child. **18**:246 (Oct.) 1919.

time of the boys. This study was made possible only because of the active interest in the boys' health taken by the principal of the school and the hearty cooperation of the parents. The matter of time distribution and the question of nutrition are the two most important factors in the health of school children.

There are many guides to the study of nutrition and there are tables of standards of normal development. There is no means at present of determining whether a given child is distributing his time in conformity with a healthful arrangement. It seemed to us that it was worth while to attempt to prepare a table of what appeared to be a reasonable and healthful division of the hours of the week. It was thought that such a table might serve in much the same way as the tables of normal weight and height are used to measure nutrition. The weight and height tables do not furnish the sole method of estimating a child's nutrition, but they do give an average standard with which the individual child may be compared.

Tables 1, 2, 3 and 4 were prepared after a study and comparison of the time distribution of the children of various school ages. The data for the tables was secured from the actual school schedules and the statements of the parents concerning the time spent at home. After the tables had been made, as many of the boys as possible were checked against them as a control. We believe that they represent very nearly the proper distribution of time for boys of the ages indicated. The figures may need to be modified later, but those entered here represent the facts as nearly as could be determined with the present information. They are submitted in the hope that they will be of use in planning the daily program of school boys. If they are tried out by many different people their value and accuracy can be determined.

In attempting to make a weekly plan for school boys, the first division of time comes between that spent at school and that spent at home. The home time is partly on school days and partly at week ends. Five days out of the seven the boys are in school, and during these days the parent and the teacher share in planning his routine. For two days at the week-end they are at home all the time and the parent alone is responsible. The particular school in which these studies were made is a country day school, so that the hours at school are long. None of the boys under 14 years of age are given home work. If a boy goes to a one session school, the figures for school days will need some adjustment to meet that situation, but the adjustment should be made taking into account all the factors and remembering also that there are seven days in the week.

The boy's time may be considered from another point of view as divided between activity and relative inactivity. His activity takes the

TABLE 1.—WEEKLY SCHEDULE IN HOURS FOR SCHOOLBOYS, AGED 6 YEARS

		School Days		Week Ends	Weekly Total	
		School	Home			
Activity	**Study**	14	0	0	14	40½
	Exercise	7	7½	12	26½	
Inactivity	**Relaxation**	10½	21	12	43½	127½
	Sleep	0	60	24	84	
Total.		31½	88½	48	168	168

TABLE 2.—WEEKLY SCHEDULE IN HOURS FOR SCHOOLBOYS, AGED 8 YEARS

		School Days		Week Ends	Weekly Total	
		School	Home			
Activity	**Study**	17	0	0	17	48½
	Exercise	8½	9	14	31½	
Inactivity	**Relaxation**	9½	18½	11	39	119½
	Sleep	0	57½	23	80½	
Total		35	85	48	168	168

TABLE 3.—WEEKLY SCHEDULE IN HOURS FOR SCHOOLBOYS, AGED 10 YEARS

		School Days		Week Ends	Weekly Total	
		School	Home			
Activity	**Study**	21	0	0	21	55
	Exercise	10	9	15	34	
Inactivity	**Relaxation**	9	16	11	36	113
	Sleep	0	55	22	77	
Total		40	80	48	168	168

TABLE 4.—WEEKLY SCHEDULE IN HOURS FOR SCHOOLBOYS, AGED 12 YEARS

		School Days		Week Ends	Weekly Total	
		School	Home			
Activity	**Study**	22½	0	0	22½	62½
	Exercise	12	12	16	40	
Inactivity	**Relaxation**	5½	15½	11	32	105½
	Sleep	0	52½	21	73½	
Total		40	80	48	168	168

form of study and exercise. His inactivity consists of sleep and relaxation. Relaxation is not a very satisfactory term, but we have been unable to find a better one to describe the time that is spent in dressing, in eating, in reading, etc. These periods require comparatively little expenditure of energy.

In the distribution of the boy's active time there is room for considerable variation, but the school curriculum makes it necessary for him to cover a certain amount of work, therefore, there is an irreducible minimum in the hours of study. Since he must have some exercise every day, there is an irreducible minimum in this factor also. How wide the variations in these two particulars may be is a matter not definitely determined. The figures which we have put down represent what the average healthy boy of a given age can do who is taking enough school work to advance in his grade and who is having sufficient exercise to keep in good condition.

In his inactive period the factor of sleep should not be below what is entered on the table. Sleep is the time during which there is a restoration of energy in the body. It acts much like the charging of the batteries which keep the electric mechanism of the automobile working satisfactorily. We cannot afford to draw too heavily on the reserves of the body. If we do, continuing the simile, our batteries will become discharged and the engine will not run.

The inactive periods should represent a balance against the periods of activity. The distribution of time between the two groups, activity and inactivity, should bear a fairly constant relation. A boy who is having a disproportionate amount of activity as compared with inactivity may be able, because of his unusual endurance, to carry through the schedule. He may be maintaining his undue activity, however, at the expense of his reserve, and eventually his health will suffer as a consequence. He may have a proportionately large amount of activity during the five school days, and yet because of an inactive week-end establish a normal weekly balance. Individual variations from the standard will undoubtedly occur, but when such variations are present, there should be some compensating consideration which would make the divergence from the average reasonable. It is possible for a child to have a weekly schedule different in every respect from the average and yet be in normal health and progress satisfactorily in school. Such a child is obviously unusual and certainly could not be taken as a model for others to follow.

We believe that the principles involved in these tables are correct. We hope that they will be used sufficiently so that correct figures may be inserted, if those given here prove to need modification. The study represents a cooperative effect on the part of teacher, parent and physician to plan the entire program of the child as a unit giving equal consideration to education and to health.

A STUDY OF PNEUMONIA IN INFANCY AND CHILDHOOD DURING RECENT EPIDEMICS *

HENRY HEIMAN, M.D.
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INTRODUCTION

During the past two years medical men have been confronted with the appalling spectacle of a most virulent epidemic that spread with terrifying rapidity over two hemispheres. The causative organism responsible for the influenza outbreak has not yet been definitely determined; but the high mortality was unquestionably due to the development of acute toxic pneumonias in a large proportion of the cases.

To the pediatrician, it seemed quite evident, early in the epidemic, that although infants and children were readily susceptible to the infection, the number that succumbed was comparatively small. Wollstein and Goldbloom,[1] however, in reporting a series of pneumonia cases in infants at the Babies' Hospital in New York City during a period of six weeks in the Fall of 1918, found a mortality of 57.7 per cent. (thirty out of fifty-two cases).

SCOPE OF PAPER

The following is an analysis of 336 cases of pneumonia admitted to the pediatric service at Mount Sinai Hospital during a period including the pandemic of 1918 and the recurrent wave of 1919. Not all of the cases were definitely influenzal in type. Most of them entered the hospital with a pneumonic process already developed, so that it was sometimes difficult to trace their origin. But the great proportion of the cases occurring during the epidemics were undoubtedly of this variety.

CLASSIFICATION OF CASES

Of 336 cases, 288 were bronchopneumonias, 48 lobar pneumonias; 56, or 16.6 per cent., succumbed. The cases of bronchopneumonia showed a mortality of 17.7 per cent. (51 our of 288 cases), and the age distribution was as follows:

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* From the Pediatric Service of the Mount Sinai Hospital.

* Read at the Thirty-Second Annual Meeting of the American Pediatric Society, held at Highland Park, Ill., May 31, June 1 and 2, 1920.

[1] Wollstein and Goldbloom, Am. J. Dis. Child. **17**:165 (March) 1919.

TABLE 1.—MORTALITY IN BRONCHOPNEUMONIA CASES

Age of Patient	Number of Cases	Number of Deaths	Percentage of Mortality
0 to 6 months..............	74	19	25.6
6 months to 1 year..........	70	14	20.
1 to 2 years................	59	7	11.8
2 to 5 years................	41	7	15.9
5 years	41	4	9.7

With the exception of the 2 to 5 year period, the mortality figures varied inversely with the age.

Of the forty-eight cases of lobar pneumonia 5, or 10.4 per cent., ended in death.

TABLE 2.—MORTALITY IN LOBAR PNEUMONIA CASES

Age of Patient	Number of Cases	Number of Deaths	Percentage of Mortality
0 to 6 months..............	0	0	0
6 months to 1 year..........	6	2	33.3
1 to 2 years................	6	1	16.6
2 to 5 years................	14	0	0
5 years	22	2	9

These figures compare very favorably with the statistics of pneumonia in infancy and childhood during previous years.

Pisek and Pease,[2] reporting 1,000 cases over a period of several years, found a mortality of 34.3 per cent.; Koplik[3] reviewed 1,351 cases admitted to the pediatric service of Mount Sinai Hospital between 1906-1914 and found a mortality of 18.3 per cent. In a report of the Babies Hospital,[4] September, 1914, of 51 patients with lobar pneumonia 5, or 10 per cent. died; of 116 cases of bronchopneumonia 62, or 33.1 per cent., ended in death.

PATHOLOGY AND BACTERIOLOGY

The left lower lobe was the most frequently involved in both lobar and bronchopneumonic cases. Holt,[5] in a report of 261 cases of bronchopneumonia, found the left lower lobe more extensively diseased than the right in more than two thirds of the cases. In our cases that came to necropsy, there were typical areas of consolidation in all stages, and hemorrhagic foci were a common finding.

Wollstein and Goldbloom,[1] from a study of the necropsy findings in eighteen cases in infants, report that the "characteristic features

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2. Pisek and Pease: Am. J. M. Sc. **151**:14 (Jan.) 1916.
3. Koplik, H.: J. A. M. A. **69**:1661 (Nov. 17) 1917.
4. Babies Hospital Twenty-Sixth Annual Report, Sept. 30, 1914.
5. Holt: Diseases of Infancy and Childhood, 1918.

were purulent infiltrations of the alveolar walls and septa, hemorrhages and suppurative bronchiolitis."

A variety of organisms were found in the sputum in our cases, where obtainable. These included the influenza bacillus, pneumococcus, streptococcus and staphylococcus, but none in sufficient preponderance to justify any definite conclusions. In ten cases the sputum was examined for type pneumococcus and revealed: Type I, two cases; Type II, one case; Type III, none; Type IV, seven cases.

In twenty-four cases, specimens of blood were examined for type pneumococcus according to the method of Loewe, Hirschfeld and Wallach,[6] and showed: Type I, four cases; Type II, six cases; Type III, none; Type IV, fourteen cases.

The precipitin test in specimens of urine showed also Type IV most frequently present. Wollstein and Benson[7] found Type IV present in 60 per cent. of the cases reported in 1916.

One of our patients, showing Type I, received specific serum intravenously but succumbed from a severe toxemia.

ROENTGEN-RAY FINDINGS

Of twenty-eight roentgenograms of the chest taken in cases of lobar pneumonia, twenty-five showed definite shadows. Of seventy-three cases of bronchopneumonia, sixty showed more or less distinct shadows, which were interpreted as infiltrations. In eight cases in which no physical signs were elicited, but presented the clinical picture of pneumonia, the roentgen ray revealed the presence of lesions in the lung. We have found the roentgen ray of invaluable assistance in the diagnosis of both types of pneumonia.

BLOOD EXAMINATIONS

Of 200 blood counts recorded among our cases, the lowest leukocyte count was 4,000, with 40 per cent. polymorphonuclears. Another showed a count of 4,100 with 44 per cent. polymorphonuclears. Both patients died. We have found that a count below 10,000 and a polymorphonuclear count below 50 per cent. is significant of very poor resistance. The highest count was 86,000 with a polymorphonuclear count of 95 per cent. in a case with rapid recovery. The average blood picture was 25,000 leukocytes with 80 per cent. polymorphonuclears. Ten blood cultures taken in severe uncomplicated cases proved sterile.

COMPLICATIONS

The most frequent complication encountered was acute otitis media, which occurred in seventy-five of our 336 cases. Both ears were involved in forty cases. In general, our policy in treatment is a conservative one. Unless there is distinct bulging, we do not incise. In private practice, we find too many membranes opened without sufficient indications.

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[6] Loewe, Hirschfeld and Wallach: J. A. M. A. **73**:170 (July 19) 1919.

[7] Wollstein and Benson: Am. J. Dis. Child. **12**:254 (Sept.) 1916.

Empyema developed in seventeen cases. We advise strongly against early operation before the acute stage of the pneumonic process has subsided. The results obtained by watchful waiting in these cases are immeasurably better than immediate operative interference on the aspiration of pus from the pleural cavity. If dyspnea becomes marked due to the rapid accumulation of purulent fluid, potain aspiration is indicated.

In eight cases meningism, characterized by rigidity of the neck, convulsions, or spasms, delirium at times and a positive Kernig developed during the course of the pneumonia. In the severe cases lumbar punctures were done to relieve the increased cerebrospinal pressure.

In three cases lethargic encephalitis complicated the picture. Recent studies by Loewe and Strauss,[8] from the pathologic laboratory of Mount Sinai Hospital, throw new light on this condition. They believe it is a distinct disease produced by a specific organism which they have isolated in a large proportion of the cases.

In one case a hemiplegia and an embolus of the right external iliac artery developed necessitating amputation of the left lower extremity.

Two cases of severe acidosis with markedly decreased carbon dioxid tension proved fatal. There were two cases of spontaneous pneumothorax and one of diffuse subcutaneous emphysema.

One case was complicated by an acute suppurative pneumococcus meningitis. Blood culture as well as cerebrospinal fluid showed the presence of Type I pneumococcus. Specific monovalent serum was injected intravenously and into the spinal canal, but without improvement. The patient succumbed about the tenth day.

One case was complicated by an acute purulent pericarditis. Blood culture was positive for Type I pneumococcus. Operation was performed, but the patient subsequently died of a continued general infection.

The rest of the complications included two cases of suppurative cervical adenitis, one of suppurative arthritis of the left shoulder, one of pyelitis in which bacillus coli was the invading organism, one gangrenous stomatitis, and one case of retropharyngeal abscess.

TREATMENT

Of prime importance in the treatment of pneumonia is the hygienic care and efficient nursing. Though much has been written about this aspect, it is still too often overlooked. A bright sunny room, with an abundance of fresh air, quiet surroundings and well trained nurses under close supervision are important essentials. A fretful, nervous mother should be excluded from the sick room. A modern hospital ward furnishes an ideal environment; but here, too, the greatest vigilance on the part of the physician must be exerted to guard against infections of the skin, eyes and mouth. A cleansing bath each morning should be a routine measure.

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[8] Loewe and Strauss: J. A. M. A. **73**:1056 (Oct. 4) 1919.

We do not favor the cold air treatment heralded several years ago with marked enthusiasm for any type of case. The gastro-intestinal tract should receive the closest attention. Milk diluted, gruels, fruit juices and an abundance of water form the chief elements of food.

Milk of magnesia in the morning and an enema each night are routine measures to insure proper elimination.

In the mild cases we have found the aromatic spirits of ammonia and liquor ammoniae anisatus useful for their mildly stimulating effect. They rarely produce any gastric disturbance. Whiskey in doses of from 10 to 20 drops, repeated every four hours, is of distinct advantage in producing temporary stimulation without the subsequent depression, which we have often seen following the administration of larger doses. Its caloric value too must be recognized.

For the moderately severe cases with high temperatures hydrotherapy, chiefly in the form of warm packs between 80 and 95 F., are employed with good results. In addition, hypodermic injections of camphor and oil, and in some cases, where irritability is not marked, caffein and sodium benzoate are indicated.

For the very toxic cases these measures are used much more intensively, more frequent hypodermic stimulation and the warm packs applied at shorter intervals. Atropin and epinephrin are used in addition, with a view to prevent edema of the lungs.

We condemn the promiscuous use of dry cupping. We regard it merely as a demonstration of spectacular therapeutics and of no real value. The excitement and exertion for the patient attendant on its use certainly decreases his resistance.

We do not recommend the general use of digitalis. We have employed it in a considerable number of patients with no appreciable beneficial results. The pulse rate is not lowered, nor is the blood pressure raised. As auricular fibrillation is a very rare complication in the pneumonias of children, its use to prevent this condition is but an ephemeral theory.

In adults, encouraging results have been reported from the use of specific antipneumococcus sera. May we not look forward to further differentiation of types of organisms in the pneumonias of infants and children with the hope of securing specific therapy?

CLINICAL DEPARTMENT

CASE OF PURPURA WITH SYMMETRICAL GANGRENE OF THE FINGERS

MAY MICHAEL, M.D.

CHICAGO

Baby Max, 2½ years old, entered Mary Thompson Hospital, June 17, 1918.

History of Illness.—Jan. 22, 1918, the child was taken ill with fever, restlessness and swelling of the glands of the neck. There was a slight sore throat and cough. During the first week of the attack large purpuric patches appeared over both upper and lower extremities. The temperature ranged between 103 and 104 F. This condition lasted about four weeks, when the purpura began to fade and the fever to subside. After an intermission of two weeks, during which the child seemed fairly well, the temperature rose again and new purpuric patches appeared, this time covering the trunk and the extremities. The second attack lasted about six weeks, the temperature ranging between 101 and 103 F. Then after a second remission for two weeks the first phalanges of all the fingers of the right hand and of the thumb, index, middle and little fingers of the left hand began to look dry and gradually turned black. This was accompanied by another rise in temperature and a breaking down of the purpuric patches, which still remained.

Physical Examination.—The child was brought to the hospital five months after the onset of the disease. Examination showed a fairly well nourished child with marked pallor. Scattered over both extremities were very pale fading purpuric lesions, varying in size from a quarter to a silver dollar; on the outer side of the left thigh was an irregular, moist gangrenous area and a corresponding area on the right buttock. The soft tissues of the first phalanx of the thumb, index, middle and little finger of the left hand were dry, atrophic, and black; the nails were intact, a similar process involved the first phalanx of the little finger of the right hand and the first and second phalanges of all the other fingers (Fig. 1). Otherwise examination revealed little of importance. The tonsils were enlarged but not acutely inflamed. There were a few enlarged cervical glands. The heart and lungs were negative, the liver and spleen were not palpable. The child seemed hypersensitive to touch and complained of pain in the joints, when these were manipulated.

Laboratory Examination.—The blood count showed 3,850,000 red blood cells; 60 per cent. hemoglobin; 20,200 white blood cells, with a differential count of 85 per cent. polymorphonuclears, 12 per cent. small lymphocytes, and 3 per cent. large lymphocytes. The Wassermann test was negative and blood cultures on several occasions failed to disclose any organism. The coagulation time of the blood was normal. The urine and stools were negative. Tuberculin tests were negative.

Course of Disease.—The child remained in the hospital from June 17 to July 6. During the first two weeks the temperature ranged between 99 and 102 F., then it gradually fell to normal. At times there was considerable pain in the joints. The patient was given salicylates, strychnin, glucose solution per rectum, and hot boric acid baths.

On dismissal the child's general condition had greatly improved. He was for the most part bright and happy and had no pain. The purpura had practically disappeared; the gangrenous areas on the thighs had healed. The fingers were practically unchanged.

Since his return home his mother has informed me by letter as to his condition. Improvement continued, though at times fever and a few purpuric patches reappeared, but it was not until February, 1919, that he regained strength enough to walk. The first and second phalanx of the first finger of the right hand and the first phalanges of all the other fingers, except the left thumb and left fourth finger, dropped off, but healed smoothly, without much scar tissue (Fig. 2). Today the child seems quite strong and except for the deformity of the fingers, shows no evidence of his illness.

COMMENT

When in the hospital, the child was seen by a number of physicians and there was considerable difference of opinion as to the etiology of the gangrene. The general opinion was that the case was one of Raynaud's disease. The absence, however, of local pallor, followed by cyanosis preceding the gangrene, the absence of intense pain in the fingers, and the association with an infectious, rather than with a trophic process, seems to eliminate Raynaud's disease.

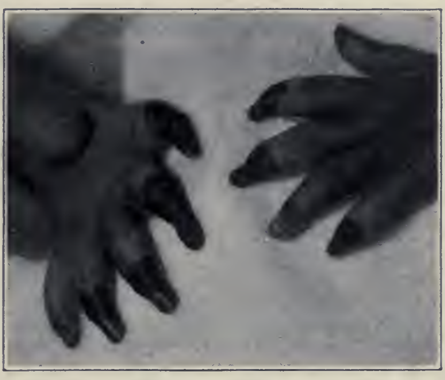

Figure 1

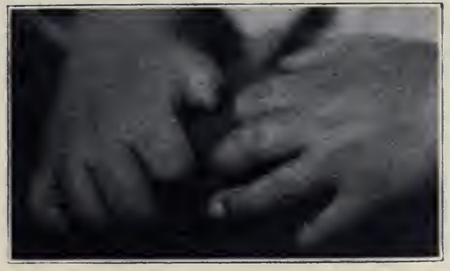

Figure 2

Ecthyma gangrenosa was considered; but in this disease the gangrene supervenes on a pustular, not a purpuric eruption and involves multiple areas of the skin and scalp.

Gangrene, associated with infectious processes, scarlet fever, measles, diphtheria, erysipelas and purpura, has long been recognized (disseminated infectious gangrene), and case reports are found scattered through the literature.[1] These reports include gangrene of the skin and extremities.[2] Munk[3] describes a case of spontaneous gangrene, resulting in the loss of several digits of the right hand, in a child of three years who had had a severe attack of measles, complicated with bronchopneumonia. He also reports a case in a 4 year old child following influenza, in which the right foot was affected. In these instances the gangrene seems to be due to an infectious arteritis.

In regard to purpura, careful search of the literature has failed to reveal a report of symmetrical gangrene of the extremities, associated with this disease, although gangrene of the purpura patches is a fairly frequent occurrence. Nevertheless, it seems probable that an infectious obliterating arteritis—the infection being the same as that which caused the purpura—is responsible for the gangrene of the fingers in the case here reported.

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[1] Hulot, J.: Traite des Maladies de l'Enfance (Grancher-Comby), Ed. 2 **4**:852.

[2] Lipes, H.: Albany M. Ann. **21**:1, 1900.

[3] Munk, J.: Arch. méd. des enf. **1**:434, 1898.

ELEPHANTIASIS CONGENITA ANGIOMATOSA (UNNA)

ASSOCIATED WITH CHANGES IN THE CAPILLARIES *

MILO K. MILLER, M.D., AND KARL M. NELSON, M.D.
CHICAGO

REPORT OF CASE

History. — R. T. B., a boy, 6 years of age, was admitted to the hospital, October, 1918, with a very marked dilatation of the veins on the right thigh leg, scrotum and penis. He is the third of five children, all the others being normal. Nothing particular is to be noted in the family history. The personal history does not contain any other feature of interest, with the exception of some deficiency in talking.

The mother noticed the swelling of the veins on the leg when the patient was 2 weeks old. When 1 year old, rubber bandages were applied, affording some relief. Such bandages have been applied at intervals since, but they were unable to prevent a gradual increase of the dilatation.

Physical Examination.—The physical examination revealed no abnormalities besides the condition of the right leg, penis and scrotum. The venous enlargement which forms tumorlike masses, beginning to the right of the scrotum, covers the entire buttocks and extends over practically the entire outer aspect of the thigh and leg, being particularly marked from the knee on down. Greatly dilated veins stand out over the dorsum, the outer aspect of the foot and extend about halfway across the plantar surface.

The swellings felt soft, elastic and velvety; over the foot they were more lobulated and "wormy." The summits of the irregularities were of a bluish color. They were turgescent but not erectile. The blood could be pressed out, leaving an apparently normal delicate skin. The tumor did not pulsate. The definition from the surrounding skin was fairly well defined. In several planes thrombi could be felt. The vascular masses became intensely engorged on standing. There was a mass of dilated deep purplish veins on the scrotum, penis and a small mass of hemorrhoidal veins (Figs. 1 and 2).

Measurements of Right and Left Leg on Standing and in Recumbent Position

	Right		Left	
	Standing, Cm.	Recumbent, Cm.	Standing, Cm.	Recumbent, Cm.
Upper half thigh	32	31	30	30
5 cm. above patella	25.5	24	23.5	23
Patella	27	26	23	23
Calf	22	20	21	20
5 cm. above malleolus	15	14	15.6	14
Dorsum foot	17.5	16.5	16	16

One small angioma about the size of a pinhead was located on the right nostril.

The blood Wassermann was negative and the eyegrounds were normal.

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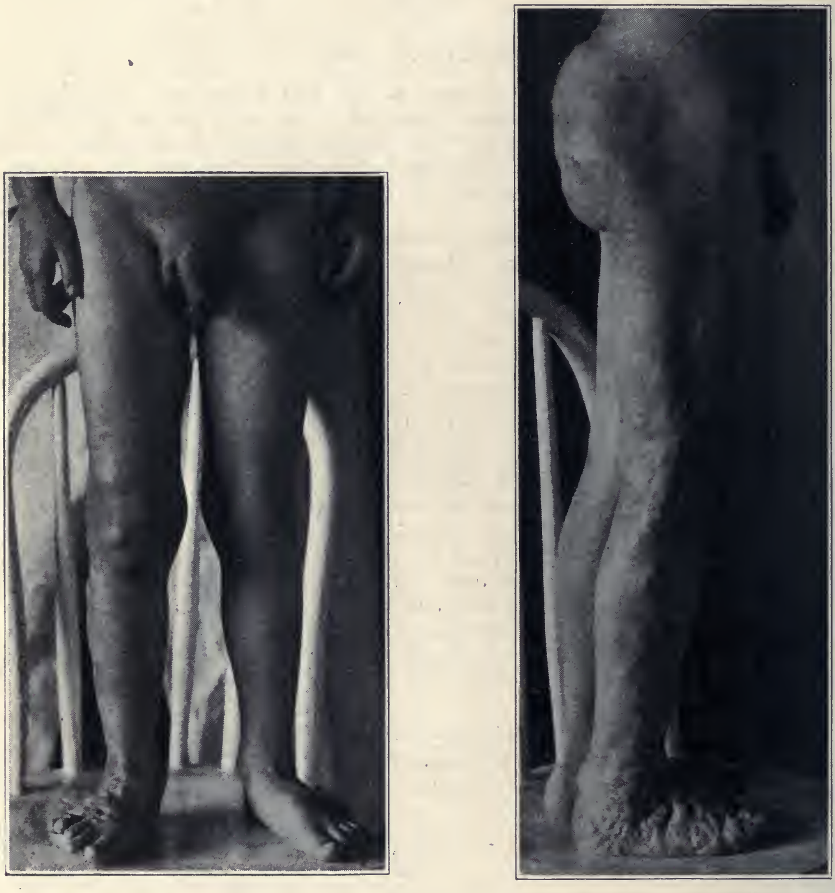
* From the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital.

COMMENT

Cases as the one described seem to be quite rare. Unna[1] quotes two cases involving chiefly one leg, but he does not give the references. Histologically, the lesions are found in the superficial layers of the corium. They may extend deeply and involve the subcutaneous tissues. The venous capillaries are chiefly involved. Thickening of the walls of the veins is followed by endothelial proliferation. Elastic fibers and muscle fibers are absent.



Figs. 1 and 2.—Anteroposterior and lateral views showing the angiomatous condition of the right leg and the genitalia.

One of the most striking features of the disease is its apparent strict localization. This made it quite natural that only factors acting locally have been considered in the etiology of these angiomas. However, it is possible that aside from causes acting locally a more general cause is to be found in a widespread abnormality of the vascular system. We availed ourselves of the method first described by Weiss [2] and later by Danzer and Hooker [3] to study the capillaries of the nailfolds of the fingers. The procedure is the following: The finger is placed on the stage of the microscope, keeping the arm in a comfortable position. We found it convenient to place the finger in a groove made in a flat cork, or in a tapering holder made of brass. The fingers have been scrubbed, dried and some cedar oil has been placed on the nailfold. A strong light is thrown on the nailfold. We used a 90 Watt nitrogen bulb and a lens of about seven inch focal length to concentrate the light on the finger. With a little practice it is very easy to find the last row of capillaries using the low power and preferably low eye-piece. The picture presenting itself is very pretty. As a rule, the capillaries appear in a row forming well defined slender loops in which the thinner arterial part is readily distinguished from the wider venous part. Sometimes the capillaries are smooth and evenly looped while others are tortuous and winding. Some form a figure 8, others are like corkscrews, etc.

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[1] Unna: The Histopathology of the Diseases of the Skin, 1896.

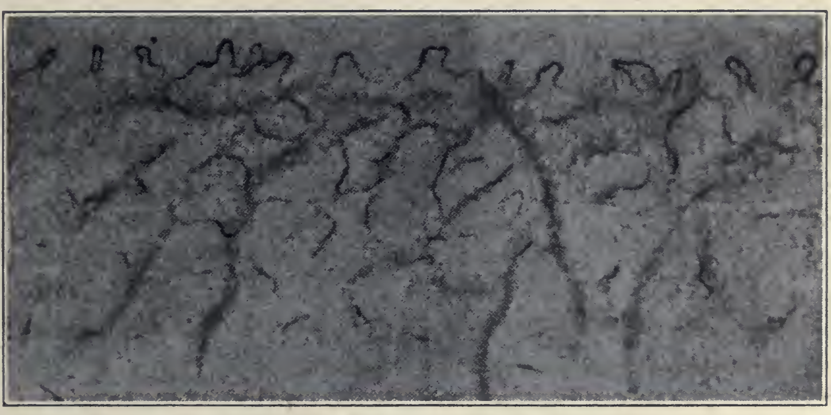

Fig. 3.—The degree of development of lymph vessels and blood vessels in early months of life.

Comparing the aspect presenting itself in our case with that of a number of children of various ages, and of adults, three striking differences were noted: (1) the loops were very irregularly arranged; (2) the number of the loops was markedly greater than in other cases; and (3) the loops were less sharply defined and not well developed. They appeared to be stunted, that is, shorter and were more uniform, forming relatively broad, more or less curved, ends. The nailfolds of the toes showed the same pitcure as that of the fingers.

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[2] Weiss: Eine neue Methode zur Suffizienz pruefung des Kreislaufs, Ztschr. f. Exper. Path. u. Therap. **19**:437, 1918.

[3] Danzer and Hooker: Determination of the Capillary Blood Pressure in Man with the Microcapillary Tonometer, Am. J. Physiol. **52**:136, 1920.

The aspect of the capillaries suggested that their development was arrested at an early stage. Holland and Meyer[4] studied the capillaries of a larger number of infants. They claim that the new-born arrives with an unfinished vascular system and uses its first months of life for the further development of its circulatory apparatus. Figure 3 is reproduced from their representation. It resembles somewhat the aspect of the capillary loops of our case. But in our case, the arrangement of the loops was much more irregular, the number of loops in a field was strikingly larger and their form showed even less variation. The observation of Mertz[5] corroborated those of Holland and Meyer, inasmuch as he saw during the first four to six weeks very short archlike loops protruding from the subcapillary vascular network. Some weeks later, the capillaries were developed further. Such pictures are not seen in every new-born. In older children and in adults they have not been described. According to Mertz, some individuals possess better developed capillaries than corresponds to the average of their age; in others, the development takes more time. In cases we have studied for comparison, including two premature infants, a number of infants during the first year of life and a large number of older children, we did not see such primitive capillaries. But Dr. K. Mayer, who continued these studies on a larger number of infants, has seen pictures coinciding with those described by Holland and Meyer, as well as by Mertz. In the two premature infants the capillaries were, comparatively speaking, remarkably well developed.

This much seems rather certain, that the capillaries of our case are abnormal for his age. We have to acknowledge the possibility that the abnormality of the vessels is a coincidence pure and simple and does not stand in any relationship to the local lesion.

But the presence of an abnormality of a part of the vascular system as in the case described, surely does suggest a relationship between this abnormality and the lesions. One can think of a direct causal relationship so that this abnormality of the vessels, in conjunction with some local factors, enters directly into the production of the lesion.

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[4] Holland and Meyer: Beobachtungen an den Hautkapillaren bei Kindern mit exudativer Diathese, München med. Wchnschr. **66**:1191, 1919.

[5] Mertz: Beobachtungen an den Haut kapillaren von Saeuglingen, Monatschr. f. Kinderh. **18**:13, 1920.

It may be said definitely that in cases of congenital angioma of the type described it is possible that a general abnormality of the vessels is one of the etiologic factors.

PROGRESS IN PEDIATRICS

A REVIEW OF THE LITERATURE OF SYPHILIS IN INFANCY AND CHILDHOOD*

PART II

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TREATMENT

The drugs most generally in favor for the treatment of syphilis are arsphenamin or an allied product, mercury or one of its salts, and iodids. There are as many methods of using these drugs as there are individuals treating syphilis. In some quarters there has been an attempt at a standardized method of treatment, and this has been more or less successful among certain groups. There can be no strictly standard treatment because there are no standard human beings. However, a closer approach to standardization would be preferable to the inadequate treatment sometimes given. The general tendency is to alternate periods of treatment with arsphenamin and mercury, with or without iodids. The periods of active treatment usually last from two to six months, or more, and are followed by a rest period of a month or more. The courses of active treatment are repeated, varying in intensity, duration and intervals depending on the progress made. Several authors [104] have recently given in detail their plans of treatment for syphilis in adults. These plans are more or less typical of the methods generally used. It is the opinion of some [105] that it is dangerous to use arsphenamin and mercury at the same time, while others combine their use routinely, apparently without mishap.[106]

An argument for short intensive courses of treatment followed by rest periods is that spirochetes may become "drug fast" by continued contact in low concentrations. That such drug fastness occurs has been shown by Akatsu and Noguchi.[107] In vitro spirochetes acquired a resistance to increasing doses of arsphenamin and mercury. This resistance was most pronounced in the case of mercury. The spirochetes lost their drug fastness when grown again in normal mediums. Neither sodium nor potassium iodid showed any marked action on spirochetes.

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* From the Department of Pediatrics, Washington University.

104. Scott and Pearson: J. A. M. A. **72**:1064 (April 12) 1919; Corbus: J. A. M. A. **73**:1658 (Nov. 29) 1919; Irvine: Am. J. Syphilis **2**:167 (Jan.) 1918; Weiss and Conrad: Am. J. Syphilis **4**:253 (April) 1920.

105. Pinard: Presse méd. **27**:249 (May 8) 1919.

106. Clark: New York State J. M. **19**:282 (July) 1919; Adams: Brit. M. J. **2**:541 (Nov. 16) 1918.

107. Akatsu and Noguchi: J. Exper. Med. **25**:349 (March) 1917.

ARSPHENAMIN

It is the general opinion that arsphenamin is more efficient than neo-arsphenamin. Schamberg[108] noted that though neo-arsphenamin is less active therapeutically, the difference is largely made up by the discrepancy in the tolerated dose. Arsphenamin is two and one-half times more toxic than neo-arsphenamin. Neo-arsphenamin was the favorite drug on both sides of the fighting front during the recent war. The ease of preparation and administration, and the smaller number of reactions are great advantages. No proof exists that in proper dose it is not as efficient as arsphenamin. Neo-arsphenamin may be given safely and advantageously in concentrated solution by the syringe method. The syringe method of administration has a very marked advantage over the gravity method in the case of infants and very young children.

Dilution of Solutions.—The total adult dose of neo-arsphenamin may be administered in 2 c.c. of water with no ill effect,[109] although the U. S. Public Health Service,[110] and others, recommend a dilution of 1:20. The best authorities recommend a concentration of arsphenamin of not greater than 1:150, the most conservative recommending a dilution of 1:300.[111] Pollitzer[112] states that 1:200 makes practically a normal solution. Kolmer and Yagle[113] have shown that a dilution of 1:200, using water as the diluent, has a marked hemolytic effect *in vitro,* while the solution was only from one-eighth to one-fourth as hemolytic if made isotonic by using salt solution as the diluent. Part of the hemolytic effect is due to hypotonicity of the water solution and part to the hemolytic activity of arsphenamin itself. Though hemolysis is not a desirable effect, it is well known that water solutions of arsphenamin are very well borne.

A number of clinicians advocate the use of concentrated solutions by the syringe method,[114] and claim no more reactions than with the more dilute solutions. Arguing against this practice, McCoy[115] states that no one knows how far the concentration of the drug and the rapidity of administration may be carried without undue risk to the patient. Collected experience shows that a very large proportion of severe or fatal reactions have been associated with high concentration and rapid administration. McCoy's technic is based on data sent to the U. S. Public Health Service by physicians reporting unfavorable results. Most of those who recommend concentrated solutions also recommend or use rapid administration. The more conservative clinicians, including the U. S. Public Health Service, use a rate of injection varying from one to two decigrams a minute, the greater the dilution the longer the time allowed.

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[108] Schamberg: J. A. M. A. **73**:1883 (Dec. 20) 1919.

[109] Young: J. A. M. A. **73**:131 (July 12) 1919; Ravaut: Presse méd. **23**:398 (Oct. 11) 1915.

[110] U. S. Public Health Service: J. A. M. A. **72**:1086 (May 10) 1919; Public Health Rep. **34**:1131, 1919.

[111] Pusey: J. A. M. A. **72**:1786 (June 14) 1919; U. S. Public Health Service: See Reference 110; McCoy: J. A. M. A. **73**:130 (July 12) 1919; Pollitzer: J. Cutan. Dis. **34**:633 (Sept.) 1916; Goldenberg: J. A. M. A. **72**:1634 (May 31) 1919.

[112] Pollitzer: See Reference 111.

[113] Kolmer and Yagle: J. A. M. A. **74**:643 (March 6) 1920.

[114] Lockhart and Atkinson: Brit. M. J. **1**:33 (Jan. 11) 1919; Nelken: J. A. M. A. **72**:1695 (June 7) 1919; Low: Colorado M. J. **14**:170 (June) 1917; Smith: J. Mich. M. Sc. **16**:165 (April) 1917.

[115] McCoy: See Reference 111.

The disodium salt of the arsphenamin base is claimed to be less toxic and to cause fewer reactions than the monosodium salt. That this is true has not yet been conclusively demonstrated. Kolmer and Yagle[113] have shown a greater hemolytic activity with the further addition of alkali. Jackson and Smith claim a greater deleterious effect on the circulation the greater the addition of alkali. The monosodium salt is formed when just enough sodium hydroxid is added to clear the solution, while the formation of the disodium salt occurs when about one-third more alkali is added. The U. S. Public Health Service[110] advocates the addition all at once of 0.9 c.c. normal sodium hydroxid per decigram for the formation of the disodium salt.

Interval of Injection.—The proper interval for arsphenamin injection is of considerable practical interest. The majority of clinicians use weekly injections largely on an empirical basis. Stühmer[116] recently asserted that the interval should be long because he found a protein substance with which an oxidation product of arsphenamin is loosely connected for seven days after administration. The elimination of arsphenamin administered intravenously is begun almost immediately. Arsenic may be detected in the urine within the first hour, and in from forty-eight to seventy-two hours more than 90 per cent. has been excreted.[117] By the end of the first hour after administration, 80 per cent. has disappeared from the blood,[118] and by the end of two or three hours it has largely become fixed in the tissues. In order to keep the blood charged for several days at a time, it is necessary to give arsphenamin at least daily. Pollitzer[117] considers it desirable to keep the blood charged in this way for several days in order that arsphenamin may reach the "dark corners" of the body which it may not do with single injections widely separated. It has

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116. Stühmer: Quoted by Bruhns and Löwenberg, Berlin klin. Wchnschr. **56**:948 (Oct. 6) 1919.

117. Goodman: Am. J. Syphilis **3**:449 (July) 1919; Pollitzer: See Reference 111; Schamberg: Quoted by Hazen, Am. J. Syphilis **2**:778 (Oct.) 1918.

118. Adler: Boston M. & S. J. **171**:900 (Dec. 10) 1914.

been Pollitzer's custom to give full doses for three successive days, and he cites Scholtz as giving three injections in twenty-four hours. Goodman[117] reports the successful use of Pollitzer's method. Sicard and his co-workers[119] give daily injections of neo-arsphenamin until 6 or 7 gm. are given (adults), keeping watch for signs of intoxication, the chief early sign of which they claim is increased urea content of the blood. Hazen[120] states that it is better to give arsphenamin at seventy-two hour intervals rather than daily, for then sufficient time is allowed to guard against dangerous late reactions. He has demonstrated that patients will stand as many as ten injections at seventy-two hour intervals with perfect impunity. Hazen states that the advisory council in venereal diseases of the surgeon-general's office has recommended an interval of five days.

Route of Administration.—Practically all syphilographers use the intravenous route for the administration of both arsphenamin and neo-arsphenamin. However, there are still those who use and advocate other routes. Trossarello[121] advocates injection into the fascia lata rather than intramuscularly. By this route only 15 per cent. have a sharp painful reaction and only 25 per cent. have a moderate reaction, while in the remaining 60 per cent. the injection is nearly painless. Azémar[122] states that an aqueous solution of neo-arsphenamin is rapidly absorbed by rectum and in the second hour is present in the urine in ponderable amount. The amount increases in the urine up to the third day and is usually absent from the urine by the sixth day. Compared to intravenous injection, the elimination is slower, the therapeutic effect less prompt, less thorough, less constant and less permanent. The adult dose used is 0.9 gm., and the interval is at most six days. There was never the slightest untoward effect. Grajewski[123] and Fihlo[124] both prefer the rectal route. Mandracchia[125] describes his method of giving an arsphenamin enema. He states he has observed no sequels.

Villarejo[126] recommends for the early treatment of inherited syphilis in infants the subcutaneous use of 1 cg. per kilogram in 5 c.c. of serum every fifteen days for three doses. Because of the slow absorption, there is less danger from massive destruction of treponemas, which may occur when a full dose is given intravenously causing a fatal result. Lesage[127] calls attention to the necessity of beginning with small doses in infancy. Likewise Ribadeau[128] emphasizes the fact that the treatment of athreptic syphilitic infants must be begun with milligrams rather than centigrams.

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[119] Sicard, Haguenan and Kudelski: Bull. d. l. Soc. méd. d. Hôp. **43**:821 (Oct. 17) 1919; abstr., J. A. M. A. **73**:1859 (Dec. 13) 1919.

[120] Hazen: Am. J. Syphilis **2**:778 (Oct.) 1918; **3**:665 (Oct.) 1919.

[121] Trossarello: Policlinico **26**:937 (Aug. 3) 1919.

[122] Azémar: Ann. de dermat. et syph. **7**:14 (Sept.) 1918.

[123] Grajewski: Urolog. & Cutan. Rev. **23**:22, 1919.

[124] Fihlo: Brazil Medico **32**:234, 1918; abstr., Brit. J. Child. Dis. **16**:122 (April-June) 1919.

[125] Mandracchia: Med. Rec. **97**:144 (Jan. 24) 1920.

[126] Villarejo: Medicina Ibera **8**:54 (July 26) 1919; abstr., J. A. M. A. **73**:1251 (Oct. 18) 1919.

MERCURY

It is generally conceded that any preparation of mercury administered in any manner is satisfactory in the treatment of syphilis, provided that it is administered in such a manner that it is absorbed in adequate amounts and in such a manner that no damage is done to the patient. The methods of administration most in favor in the intensive treatment of syphilis are by inunction and by intramuscular injection. Some few prefer the intravenous route, but this has the disadvantage of ultimately producing a sclerosis of the vein used no matter what form of mercury is selected. McDonagh[129] recommends the intravenous injection of colloidal mercury, claiming a more rapid symptomatic result than with arsphenamin. The diarrhea, tender gums and abdominal pain which are likely to result may be obviated by the injection of intramine.

Because calomel ointment is more cleanly as an inunction than mercurial ointment, it would be preferable if shown to be effective. Observations on this point have been made by several clinicians. Schamberg[130] found that calomel ointment in the strength used by him was fully as well absorbed and as effective as mercury ointment. Wile and Elliott[131] showed a much better absorption with mercury than calomel ointment. Cole and Littman[132] found calomel inunctions, in the dose ordinarily recommended and used. almost totally inefficient against the visible lesions of syphilis. Signs of absorption (salivation and gingivitis) in appreciable quantity were largely absent.

Schamberg[133] found that the insoluble preparations of mercury, such as gray oil, calomel and mercury salicylate, when given intramuscularly, are absorbed at the rate of a little over 1 per cent. of the injected amount per day. Even at the end of six or seven weeks almost 50 per cent. of the injected mercury may be unabsorbed. He concludes that the injection of the usual doses of insoluble mercury

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127. Lesage and Kouriansky: LeNourrison **7**:193 (July) 1919.

128. Ribadeau: Dumas and Faroy, LeNourrison **7**:146 (May) 1919.

129. McDonagh: Lancet **1**:914 (June 16) 1917.

130. Schamberg, Kolmer, Raiziss and Gavron: J. A. M. A. **70**:142 (Jan. 19) 1918.

131. Wile and Elliott: J. Cutan. Dis. **35**:594 (Sept.) 1917.

132. Cole and Littman: J. A. M. A. **73**:1409 (Nov. 8) 1919.

133. Schamberg, Kolmer and Raiziss: Am. J. Syphilis **1**:1 (Jan.) 1917.

compounds at weekly intervals in the human subject must invariably lead to an accumulation of the drug in the tissues. Ramsay and Ziegler,[134] working with infants and children, found that the skin readily absorbs mercury with or without rubbing, and that mercury continues to be eliminated in the urine for a considerable time. The maximum excretion occurred in the second twenty-four hours. With continuous inunctions there is an accumulation in the system, and considerable amounts are eliminated at intervals with only traces between. Both mercury salicylate and mercury bichlorid given by injection are eliminated in appreciable amounts for eight days or longer, the daily amounts varying widely. Calomel, 0.016 gm., every two hours for four doses, and gray powder, 0.03 gm., every three hours for three doses, continue to be eliminated in the urine for nine days. The maximum amount is eliminated during the second twenty-four hours. They conclude that it is probable that the daily use of any mercury salt in the amounts usually prescribed is unnecessary and presumably harmful.

Wile and Elliott[131] found that mercury is eliminated readily and in appreciable quantity by way of the milk. This was found to be the case after inunction and after injection, and is, therefore, presumably true for any effective form of mercury treatment.

POTASSIUM IODID

No new observations in regard to potassium iodid in syphilis have been noted. The interesting observations of Jobling and Peterson[135] in regard to the antefermient action of iodids are prior to the time limits of this review. Fordyce[136] makes the statement that in bone and periosteal lesions attended by severe pain there is no drug in the pharmacopeia that produces so rapid an effect in relieving pain and neoplasm as potassium iodid.

OTHER REMEDIES

The use of colloidal silver has been advocated by Notthaft.[137] He has used two preparations, fulmagen and electrargol, intravenously, in 2 per cent. solution, increasing the dose from 1 to 10 c.c. He claims good results and but little reaction.

Sulpharsenol is a new antisyphilitic remedy which has been tried in thirty-three cases of human syphilis by Levy-Bing and his

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134. Ramsay and Ziegler: Am. J. Dis. Child. **16**:229 (Nov.) 1918.

135. Jobling and Peterson: Arch. Int. Med. **15**:286 (Feb.) 1915.

136. Fordyce: Am. J. M. Sc. **152**:469 (Oct.) 1916.

137. Notthaft: Dermat. Wchnschr. **68**:25, 1919; abstr., Berl. klin. Wchnschr. **56**:709 (July 28) 1919.

co-workers.[138] It is composed of the base arsphenamin and a molecule of acid sulphite of sodium united by glycol. The advantages claimed are diminished toxicity, stability of solutions, perfect tolerance, and great therapeutic activity. The effect on the visible lesions was rapid. It can be administered subcutaneously or intramuscularly with but little local pain. The effect on the Wassermann reaction remains to be determined.

The virtues of silver-salvarsan-sodium have been highly extolled in the German literature. Kolle[139] first experimented with this substance on the syphilis of rabbits and found it more active than arsphenamin and less toxic. The therapeutic dose contains from one-third to one-half of the amount of arsenic in the older preparations, and at the same time is superior in therapeutic efficiency. Kolle states that silver acts chemically as a catalyzer of the arsenobenzol molecule, and biologically as the reenforcer of the specific action of arsenic on spirochetes. The way spirochetes take silver stains suggests a special affinity. The reports of the use of this drug in human syphilis are numerous. Gennerich[140] reports that the only ill effects in more than 1,000 injections were slight cyanosis in two patients. He states that the lower toxicity in connection with the increased therapeutic efficiency is remarkable. Delbanco[141] reports 550 injections in 120 patients with no ill effects, but with prompt subsidence of manifestations. Lenzmann[142] reports that children take this drug well, and that the effect on spirochetes as controlled by the dark-field is good. Ylppö[143] also obtained excellent results in hereditary syphilis. He reports apparent permanent cure after twenty-five or thirty-five injections over a period of from three-quarters to one and one-half years. Riecke[144] reports a fatality in a man of 41 after the seventh dose of silver-salvarsan. Severe general dermatitis occurred, followed by pneumonia and death. Hemorrhagic nephritis was found at necropsy. Gennerich[145] reviewed the situation in regard to the history, the value and manner of use of this preparation. Mercury is not used in the treatment when silver salvarsan is given.

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138. Levy, Bing, Lehnhoff-Wyld and Gerbay: Ann. d. mal. ven. **14**:520, 1919; abstr., Med. Sc. **1**:394 (Jan.) 1920.

139. Kolle: Deutsch. med. Wchnschr. **44**:1177 (Oct. 24) 1918.

140. Gennerich: Deutsch. med. Wchnschr. **44**:1243 (Nov. 7) 1918.

141. Delbanco: Deutsch. med. Wchnschr. **45**:150 (Feb. 6) 1919.

142. Lenzmann: Deutsch. med. Wchnschr. **45**:355 (March 27) 1919.

143. Ylppö: Therap. Monatschr. **32**:155 (May) 1918.

144. Riecke: Med. Klin. **15**:329 (April 6) 1919.

145. Gennerich: Berlin klin. Wchnschr. **56**:769 (Aug. 18) 1919; **56**:803 (Aug. 25) 1919.

Margosic acid and its salts are reported by Chatterji[146] to clear up manifestations of syphilis rapidly, and to tend to make the Wassermann reaction negative.

Vanadium and its salts are claimed by Proescher, Seil and Stillians[147] to have a marked effect on spirochaeta pallida, and to be capable of curing syphilis in rabbits. This property is a function of the amount of vanadium injected and is independent of the constitution of the vanadium salt used. Sodium hexavanadate is a soluble neutral salt, stable and readily sterilized in solution. It is irritating when given subcutaneously or intramuscularly, but is well tolerated intravenously. When administered to human syphilitics, vanadium salts have a specific action on the disease, clearing up the clinical manifestations and favorably affecting the Wassermann reaction.

An arsonic acid derivative (N-phenylglycine-p-arsonic acid) has been described by Jacobs, Heidelberger, Brown and Pearce[148] which has a marked therapeutic action in the experimental trypanosomiasis in mice, rats and guinea-pigs. The curative ratio is small. Promising effects were noted in experimental infections with spirochetes of the recurrens group and with spirochaeta pallida. The drug does not possess a considerable degree of spirocheticidal action, but its chief effect is seen in the peculiar way it modifies or controls the course of these infections.

TREATMENT: MISCELLANEOUS

Possek[149] studied the effect of nonspecific therapy on syphilitic eye lesions. He noted that the subcutaneous injection of typhoid vaccine aids the specific treatment considerably.

Lamb[150] used successfully subconjunctival injection of arsphenaminized serum in the treatment of iritis, iridocyclitis, kerato-iritis and interstitial keratitis.

Balzer[151] describes the work of the Welander asylums in Sweden, Norway and Denmark, where syphilitic children are given a home for a period of one to four years, during which time collective treatment is administered. This is the only way to insure that treatment will be continued systematically and long enough. Paris has one institution approximating the Welander asylums.

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[146] Chatterji: Indian M. J. **53**:377, 1918; abstr., Am. J. Syphilis **3**:334 (April) 1919.

[147] Proescher, Seil and Stillians: Am. J. Syphilis **1**:347 (April) 1917.

[148] Jacobs and Heidelberger: J. Exper. M. **30**:411 (Nov.) 1919; Pearce and Brown: J. Exper. M. **30**:417, 437, 455, 483 (Nov.) 1919.

[149] Possek: Wien. klin. Wchnschr. **32**:753 (July 17) 1919.

[150] Lamb: Am. J. Syphilis **1**:58 (Jan.) 1917.

[151] Balzer: Bull. d. l'Acad. de méd. Par. **81**:811 (June 17) 1919.

TREATMENT OF NEUROSYPHILIS

In the treatment of neurosyphilis, the presence of antisyphilitic agents in the cerebrospinal fluid has been considered necessary or at least highly desirable for the adequate control of the disease. In the case of mercury, there is apparently no penetration into the cerebrospinal fluid no matter what form of treatment is tried, or even if mercury is taken in lethal dose.[131] Finlayson[152] found only a trace of mercury in 500 c.c. of cerebrospinal fluid pooled from patients with paresis receiving inunction treatment.

After the intravenous adminstration of arsphenamin, arsenic has been found in the cerebrospinal fluid by various observers. As simple as it would seem to determine the frequency and amount of arsenic penetration into the cerebrospinal fluid, there occurs a considerable difference of opinion or difference in results as to this point. It is the observation of some that penetration invariably occurs,[153] of others that it occurs in 30 per cent.,[154] and of still others that it occurs in 43 per cent.[155] These variations may have depended on the degree of meningeal reaction to syphilis, as will be discussed later. Kaliski and Strauss[156] cite determinations to show that arsphenamin reaches the cerebrospinal fluid in amounts not only equal to but often greater than that which can be given intraspinally with safety.

Though arsphenamin, when administered intravenously, is not excreted from the body for from forty-eight to seventy-two hours,[117] it has largely disappeared from the blood and become fixed in the tissues in two to three hours after administration. By one hour after injection 80 per cent. has disappeared from the blood.[118] There is then but a short period during which there is opportunity for arsphenamin to penetrate to the cerebrospinal fluid from a single intravenous injection and the maximum concentration in the fluid is probably reached in the first hour. The results of Rieger and Solomon[154] tend to verify this assumption.

Various methods of increasing the frequency of penetration of arsphenamin to the cerebrospinal fluid after intravenous injection have been tried. Some have claimed that drainage of the spinal canal shortly after the intravenous injection increases the penetration,[157] and others[155] claim that drainage has no effect or even decreases the frequency of penetration. Irritation of the meninges, either by the injection of serum or of an inflammatory process, lets down the barrier between the blood and the cerebrospinal fluid. This has been shown for immune bodies[158] and for arsphenamin. Mehrtens and MacArthur[155] found penetration of arsphenamin in 92 per cent. when the intravenous administration of the drug was preceded by intrathecal injection of normal serum. Up to the present no method has been found to increase the frequency of adequate penetration to 100 per cent. Further, Mehrtens and MacArthur state, and it is apparent from a table published by Myers,[159] that with successive intravenous injections the cerebrospinal fluids in general show progressively smaller amounts of arsenic for the same time interval.

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[152] Finlayson: Am. J. Insan. **74**:603 (April) 1918.

[153] Sachs: J. A. M. A. **69**:681 (Sept. 1) 1917.

[154] Rieger and Solomon: J. A. M. A. **71**:15 (July 6) 1918.

[155] Mehrtens and MacArthur: Arch. Neurol. & Psychiat. **2**:269 (Oct.) 1919.

[156] Kaliski and Strauss: Am. J. Syphilis **2**:609 (Oct.) 1918.

[157] Barbat: J. A. M. A. **70**:147 (Jan. 19) 1918.

It seems apparent from the laboratory point of view, as it also seems clinically, that at least occasionally cases are encountered in which it is desirable to introduce the therapeutic agents directly in contact with the central nervous system. It is on this basis that the methods of Swift and Ellis, of Ogilvie and of Byrnes have their origin. The introduction of simple solutions of arsphenamin or neo-arsphenamin into the subarachnoid space causes marked irritation and has been shown to be dangerous. Further, the combination of arsphenamin with serum is not only less irritating, but is a more potent agent than a simple solution. This combination becomes a still more potent agent after specified periods of incubation.[160] Sachs, Strauss and Kaliski[161] have shown that serum arsphenaminized in vivo by the Swift-Ellis technic contains such a small amount of arsenic as to be negligible as a spirocheticidal factor. Kaliski and Strauss[156] also state that even when serum is fortified by the Ogilvie method, concentration in the cerebrospinal fluid, sufficient to affect spirochetes, is not reached. Sachs[162] gives as his opinion that intraspinal therapy is essentially useless and theoretically unsound. Fordyce,[163] on the other hand, is a strong advocate of the usefulness of these procedures, and his clinical experience lends weight to his opinions.

The advocates as well as the opponents of subarachnoid therapy admit that many patients are benefited or "cured" by intravenous and intramuscular treatment alone. Kaliski and Strauss[157] at the conclusion of their collected arguments against subarachnoid therapy state that in their opinion the only indication for the use of intraspinal treatment is in cases with positive findings in the cerebrospinal fluid where intensive intravenous arsphenamin and mercury treatment has been given a thorough trial and found ineffectual in a period of from six months to a year. This attitude is not so very different from that of the majority of those who resort to this method of treatment. Clinical and serologic cures of neurosyphilis are frequent without resort to subarachnoid therapy. However, it seems evident that some form of intrathecal medication is in some cases necessary and in others desirable. The choice of methods is largely a matter of personal opinion and experience. Fordyce[163] uses a combination of the Swift-Ellis and Ogilvie methods. Nicholson[164] uses a combination of the Swift-Ellis and Byrnes methods. Lafora[165] and Howard[166] use a combination of the Ogilvie and Byrnes methods. Neyman and Brush[167] alternate treatments with arsphenaminized serum and mercurialized serum. All of the observations mentioned have been made in connection with adults. No detailed reports of similar observations in childhood have been found. Jeans[168] states that children with neurosyphilis can be treated with safety by the same intensive methods that are used for adults with acquired syphilis.

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[158] Amoss and Eberson: J. Exper. M. **29**:597 (June) 1919.

[159] Myers: Public Health Rep. **34**:881, 1919.

[160] Swift: J. Exper. M. **24**:373 (Oct.) 1916; Ogilvie: Am. J. Syphilis **1**:509 (July) 1917.

[161] Sachs, Strauss and Kaliski: Am. J. M. Sc. **148**:693 (Nov.) 1914.

[162] Sachs: Arch. Neurol. & Psychiat. **1**:277 (March) 1919.

[163] Fordyce: J. A. M. A. **69**:1482 (Nov. 3) 1917; Am. J. Syphilis **3**:337 (July) 1919.

Sharpe[169] has used intraventricuular injections of arsphenaminized serum in adults with paresis. He feels that this route is superior to intraspinal administration. In experimental work he found that when staining solutions were injected intraspinally but a small part reached the cerebral cortex, while the solution spread over the entire cortex both of the brain and cord when introduced into ventricles. Cotton and Stevenson[170] recommended placing the serum beneath the dura in the cranium. In this connection it might be well to mention that Wegeforth, Ayer and Essick[171] described the procedure of the puncture of the cisterna magna. They claim this route of reaching the upper fluid reservoirs is safe for clinical use in skilled hands. Direct application of antisyphilitic remedies to the central nervous system by any other than the intraspinal route has but few advocates.

The interval for intraspinal treatments depends on the reaction of the patient. Since the Swift-Ellis method causes less reaction than the others, it can be repeated more frequently. Some clinicians give it as often as once a week. Swift[172] states that it is better borne if not repeated more often than once in two weeks. He also states[173] that combined intravenous and intraspinal treatment is more active than either form alone. This corresponds to the statement of Amoss and Eberson,[159] that the concentration of meningococcic agglutinins remains high in the cerebrospinal fluid for a longer period with combined intraspinal and intravenous administration than with either method of administration singly. Ogilvie[161] uses an interval of two weeks for the stronger additions, and of ten days to one week for the weaker additions. Haller[174] states that the irritating effect of 0.001 gm. mercury bichlorid in serum is greater than 20 c.c. of serum arsphenaminized by the Swift-Ellis method, and that unpleasant symptoms are more common with mercurialized serum. Because of this greater irritation, as rapid repetition as with arsphenaminized serum is not possible. Haller states that it is particularly in cases of active syphilis of the meninges that mercurialized serum is useful.

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[164] Nicholson: Am. J. Syphilis **3**:669 (Oct.) 1919.
[165] Lafora: Rev. Neurol. **26**:625 (Aug.) 1919.
[166] Howard: Northwest Med. **18**:19 (Feb.) 1919.
[167] Neyman and Brush: Arch. Int. Med. **22**:245 (Aug.) 1918.
[168] Jeans: Am. J. Dis. Child. **18**:173 (Sept.) 1919.
[169] Sharpe: Am. J. Syphilis **2**:1 (Jan.) 1918.
[170] Cotton and Stevenson: J. Nerv. & Ment. Dis. **47**:262 (April) 1918.
[171] Wegeforth, Ayer and Essick: Am. J. M. Sc. **157**:789 (June) 1919.
[172] Swift: Am. J. M. Sc. **152**:490 (Oct.) 1916.
[173] Swift: Am. J. Syphilis **1**:524 (July) 1917.

The proper manner of treatment of neurorecidives is still in dispute. There are those who advise against arsphenamin in such an event on the basis that arsenic makes the neuritis worse. On the other hand, the evidence is that the neuritis is due entirely to syphilis and not at all to arsenic. In such case the administration of arsphenamin should prove useful. Davis[175] claims that the occurrence of nerve involvement during the course of arsphenamin treatment is not incrimination of the remedy, but an indictment of the technic. Either the dose is not large enough, not frequent enough, or continued sufficiently long. Zeissl[176] states that he has seen no nerve injury by arsphenamin in 4,000 treated cases and he does not believe that it occurs. He states also that damage to the nerves by mercury has been reported.

REACTIONS AFTER ARSPHENAMIN

A number of recent publications have reviewed the nature and causes of reaction following arsphenamin, and at the same time have proposed theoretical considerations which open up new fields for study. A brief résumé would seem worth while. The following is a clinical classification of these reactions taken largely from Schamberg,[177] with additions from various sources as noted.

Group 1: *Immediate Symptoms.*—Complaint is made of a disagreeable taste; marked redness of the cheeks and ears occurs. The lips become bright red, perhaps tinged with violet. Sometimes the redness is succeeded by a cyanotic color. In case of severe reactions there is swelling of the lips, tongue and eyelids, injection of the conjunctivae and lacrimation and an anxious expression of the countenance. Nausea, vomiting or retching followed by profuse perspiration is frequent. There may be a feeling of suffocation or air hunger with cough, respiratory embarrassment and dyspnea. The pulse is at first full and bounding, later slow and of small volume with pallor. There may be syncope with loss of consciousness and scarcely palpable pulse. Death rarely occurs. These symptoms may subside spontaneously in fifteen to thirty minutes and nothing else happens; or after a brief period of several hours the next group appears. This group of immediate symptoms seems to be of frequent occurrence. To it have been applied the terms "nitritoid crisis," anaphylactoid reaction, vasomotor and angioneurotic reactions.

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[174] Haller: Arch. Int. Med. **19**:997 (June) 1917.

[175] Davis: Urol. & Cutan. Rev. **22**:631, 1918.

[176] Zeissl: Berl. klin. Wchnschr. **56**:150 (Feb. 17) 1919.

[177] Schamberg, Kolmer and Raiziss: J. Cutan. Dis. **35**:286 (May-June) 1917.

Group 2: *Early Symptoms.*—Chilliness or rigor, headache, vertigo, nausea, vomiting, diarrhea and a temperature of from 100 to 102 F. may occur. These may be mild or severe in any particular. Occasionally pain in the back and legs. These symptoms pass off in from twelve to twenty-four hours, followed by a feeling of lassitude or weakness. Rarely urticarial, scarlatinoid, morbilliform or purpuric eruptions may appear. These disappear in a day or two. This group is not so common as Group 1.

Group 3: *Late Symptoms.*—These are referable to the brain, liver or skin.

Brain: All apparently goes well until the third or fourth day after injection, when there develops suddenly, and with a rapid course, headache, vomiting, extreme agitation, muscular twitching, epileptiform convulsions (tonic, clinic or both), dilatation of the pupils, absent reflexes, coma and death in from twenty-four to forty-eight hours after onset. The coma is usually associated with facial congestion and elevation of the temperature. At necropsy, disseminated punctiform hemorrhages are found throughout the brain. No evidence of necrosis, suppuration or softening is found. Marked edema separates the nerve fibers. The brain cells are apparently normal. Milian[178] claims that this hemorrhagic encephalitis has the same cause as the nitritoid reaction, and that patients who develop it had a nitritoid crisis at the time of injection. Milian chooses to call this condition "serous apoplexy." Blanton[179] recently reported the necropsy findings of four cases of this disorder.

Liver: Severe jaundice, accompanied, as a rule, by fever may have its onset from three days to several weeks after arsphenamin injection. Most cases run a favorable course, but exceptionally death results with the symptoms and findings of acute yellow atrophy.

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[178] 178. Milian: Paris méd. **9**:261 (April 5) 1919. Quoted by Beeson, Reference 184.

[179] 179. Blanton: Am. J. Syphilis **3**:648 (Oct.) 1919.

Skin: Persistent eruptions on the skin may be observed in from six to ten days after arsphenamin administration. Cases of universal exfoliating dermatitis have been reported. This condition persists for weeks with fever and debility and sometimes with a fatal result.[180]

Herxheimer reactions differ from those described above in that they appear within from twenty-four to thirty-six hours after injection, and consist of an aggravation of symptoms or lesions already present. Ehrlich ascribes the Herxheimer reaction to inadequate action of the drug which serves to irritate and not to kill. Neisser is undecided whether this is the reason or whether it is due to the death of the spirochetes and the freeing of toxins. At present the Herxheimer reaction is used to explain the provocative Wassermann reaction. Hesse[181] claims that the Herxheimer reaction is not specific for syphilis nor for any certain agent, but that it is due to a vasotropic action of certain drugs causing injury to the vessel wall. He has observed a Herxheimer reaction in nonspecific skin diseases after arsphenamin.

CAUSES OF REACTIONS AFTER ARSPHENAMIN[182]

1. Factors relating to the technic, including the purity of the water used, the temperature of the solution, the acidity or alkalinity of the solution, concentration, rapidity of administration and the preparation of the patient.

2. Factors relating to the drug itself (arsenoxid and "substance X").

3. Factors relating to the patient. Two patients may get the same solution with a reaction in one and none in the other. There is undoubtedly a factor of individual susceptibility. These factors may be classified conveniently into the following divisions: (a) The temperament of the individual; a terrible ordeal for one may be only an incident to another. (b) Status of infection; temperature reactions are more frequent in the florid stage. (c) Reactions may bear some relation to the integrity of the various organs. (d) Dependent on increased globulin content in the blood of syphilitics (Berman,[183] Danysz[184]). (e) Possibly sensitization of the patient by previous injection — Swift,[185] Stokes.[186]

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[180] Latham: J. A. M. A. **73**:14 (July 5) 1919.

[181] Hesse: Wien. klin. Wchnschr. **32**:439 (April 24) 1919.

[182] Guy: J. A. M. A. **73**:901 (Sept. 20) 1919.

[183] Berman: Arch. Int. Med. **22**:217 (Aug.) 1918.

[184] Danysz: Ann. d. l'Inst. Pasteur **3**:114, 1917. Quoted by Beeson, Am. J. Syphilis **3**:129 (Jan.) 1919.

[185] Swift: J. A. M. A. **59**:1236 (Oct. 5) 1912.

[186] Stokes: J. A. M. A. **72**:241 (Jan. 25) 1919.

1. *Factors Relating to the Technic.*—The use of nondistilled or old distilled water increases toxicity.[177] There may be symptoms from having solutions too hot or too cold and from failure to prepare patients, though the preparation of the patient seems to have less to do with reactions than was formerly thought.[182] Most observers agree that reactions are more frequent when solutions are more concentrated than 1 : 150 (see under treatment). That the harmfulness of concentrated solutions may be due to either a human or a syphilitic factor is indicated by the fact that Schamberg,[177] working with white rats, found that increasing the concentration did not augment the toxicity. Joseph [187] showed that alkaline solutions, whether strong or weak, in large dose or small, rapidly or slowly given, had no bad effects. Schamberg[177] also showed, using white rats, that an excess of alkali *per se* does not increase toxicity until an amount approximating from 2 to 5 c.c. of a 15 per cent. solution to one hundred c.c. was added in excess of the neutralization requirements. The monosodium salt of the arsphenamin base is held to be more toxic than the disodium salt. Failure to neutralize the solution increases its toxicity from 50 to 60 per cent.[177] The toxicity of acid solutions is proportionate to the concentration.[188] If highly diluted — 6 dg. in 300 c.c. — there is no ill effect, but in more concentrated solution there is produced a precipitate in the blood which is actually visible in the lungs and right ventricle.[187] In vitro a strength of 0.1 per cent. has no effect, but 1.0 per cent., or more, causes a precipitate so pronounced as to cause the blood to lose its fluid nature. The weight of this precipitate varies directly with the acidity and concentration.[189] From Mexico City comes the report [190] of the administration of 3 dg. of arsphenamin in 15 c.c. of water, unneutralized, resulting in acute dyspnea leading to death in about five minutes. At necropsy multiple emboli were observed in both lungs.

2. *Factors Relating to the Drug.*—Arsphenamin oxidizes easily to form arsenoxid with a higher toxicity than arsphenamin. This oxidation is most active in alkaline solution and least active in the dry powder. Ehrlich [191] believed that in hemorrhagic encephalitis arsenoxid played an important rôle and thought it probable that irritated vessels only undergo such colossal dilatation when epinephrin is present in insufficient amount. Schamberg [177] does not believe the toxicity of

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[187] Joseph: J. Exper. M. **14**:83, 179, 1911. Quoted by Berman, Reference 183.

[188] Am. J. Exper. M. **14**:248, 497, 1911; Arch. Int. Med. **8**:169, 1911. Quoted by Schamberg, Reference 177.

[189] McKee: Quoted by Berman, Reference 183.

[190] Letter to J. A. M. A. **74**:190 (Jan. 17) 1920.

[191] Ehrlich: Quoted by Beeson, Reference 184.

arsenoxid is anything like what has been claimed, nor that this substance is responsible for the reactions following arsphenamin injection. He believes there is another impurity, "substance X," which is responsible for the vasoparesis causing vasomotor symptoms. He is of the opinion that the most important factor in the causation of these reactions is referable to the drug. However, there is no convincing evidence that the drug itself is alone responsible for the reactions observed.

It is agreed by practically all observers that epinephrin will prevent a nitritoid crisis, and, the symptoms once having appeared, it will abort the attack. By energetic treatment with epinephrin, Milian [192] has saved an otherwise hopeless case of hemorrhagic encephalitis in which on the second arsphenamin injection the deepest coma ensued. He claims that both the nitritoid crisis and encephalitis are due to the vaso dilating action of arsphenamin. Sée [193] and Bory [194] each report a case of hemorrhagic encephalitis in which death resulted in spite of epinephrin and bleeding. Hirano,[195] after several years work on these reactions, concludes that they are due to the action of the drug on the suprarenals. Arsphenamin causes marked reduction in chromaffin substance of the suprarenals and the epinephrin content of the blood and the gland is markedly diminished after even a therapeutic dose. This reduction of epinephrin is immediate and sudden and the supply may not always be made up.

Hanzlik and Karsner [196] conclude from animal experiments that arsphenamin, even in a small dose, injures the circulation. The right heart becomes dilated and pulmonary congestion and hemorrhage occurs. The respiratory symptoms which occur are due to this circulatory injury and have no relation to anaphylaxis. Jackson and Smith [197] also found dilatation of the right heart which they attributed to a rise of pulmonary arterial pressure, and to the action of alkali on the heart. It is their opinion that the increase in pulmonary pressure is due to the direct stimulation of the pulmonary arterioles, and that embolus formation plays no part. They found that the more alkali that is added to the solution the greater the pulmonary pressure. Associated with the pulmonary rise there was a marked fall in the systemic pressure. Hanzlik and Krasner [198] believe that the beneficial effects of atropin and epinephrin in this instance are due to circulatory improvement.

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[192] Milian: Ann. d. mal ven. **14**:193, 1919; abstr., Med. Sc. **1**:392, 1920.

[193] See: Ann. d. mal. ven. **14**:340, 1919; abstr., Med. Sc. **1**:393, 1920.

[194] Bory: Bull. et mém. Soc. méd. d. hôp. de Par., 1919; abstr., Med. Sc. **1**:393 (Jan.) 1920.

[195] Hirano: Kitasato Arch. Exper. M. **3**:1 (April) 1919.

[196] Hanzlik and Karsner: J. Pharmacol. & Exper. Therap. **14**:379 (Jan.) 1920.

[197] Jackson and Smith: J. Pharmacol. & Exper. Therap. **12**:221 (Nov.) 1918.

[198] Hanzlik and Karsner: J. Pharmacol. & Exper. Therap. **14**:425 (Jan.) 1920.

Jackson and Smith also believe that the beneficial effect of epinephrin is due to its action on the heart, but believe that tyramin is a safer drug.

3. *Factor Relating to the Patient.*—There is some evidence that there are changes in the blood protein in syphilis as evidenced by the various coagulo reactions. Acid solutions of arsphenamin have been shown to produce precipitates in the blood, and it is thought that the protein is involved in this precipitation. It is the idea of some investigators that alkaline solutions of arsphenamin produce a similar precipitate in certain individuals and that this is more likely to occur if the drug is administered rapidly in small volume. It is also their idea that the reactions are largely dependent on this precipitation. Berman[183] found eleven patients with nitritoid reactions among 300 arsphenamin injections. Alkaline arsphenamin solution added in vitro to the serum of the non-reactors produced no precipitate, while a heavy whitish yellow precipitate was produced in the serum from each of the eleven reactors. He thinks the precipitate is responsible for the local vasodilatations which constitute the essence of the crisis. Blood from two of the reactors showed an increased protein content which was essentially an increased globulin content. Danysz[184] believes the symptoms are due to a temporary arrest of the precipitate in the capillaries and to capillary dilatation. The precipitate is a result of combination of arsenical salts with calcium phosphates in the plasma. If it is redissolved early the symptoms disappear; if slowly, then epileptic seizures and coma occur.

Stokes[199] has prevented nitritoid crises successfully by the use of atropin, fifteen minutes before the injection. He used atropin on the basis that the nitritoid reaction is an anaphylactic phenomenon. He states that injection of any powder into the blood produces anaphylactic shock; that arsphenamin solution is essentially colloidal and on injection there occurs a precipitation either of the drug from its colloidal solution or of the colloids of the plasma by the drug or by an impurity. The fallacy of these statements is pointed out by Hanzlik and Karsner[196] who show that the injection of nonprotein materials into the blood does not produce anaphylaxis even though the respiratory symptoms may simulate this condition.

REACTIONS IN RELATION TO THE LIVER

There is some dispute as to the cause of jaundice following the use of arsphenamin. Milian[200] claims that arsphenamin has no affinity for the liver, and that the jaundice is due to the action of syphilis on the liver. He treats the condition successfully by increasing the arsphenamin therapy. Sicard and his co-workers[201] denounce this statement of Milian and present evidence that the jaundice is due to the drug. Arsphenamin treatment was suspended for all cases but one, and this one was the only fatal case. In two cases the drug was being given for disease other than syphilis. Giroux[202] states that the jaundice occurring in the secondary stage of syphilis is accounted for by the fragility of the red blood cells, the jaundice being hemolytic in origin. Chabrol and Khoury[203] emphasize the importance of a predisposition on the part of the liver as a factor in toxic jaundice from arsphenamin. They ask how else than by toxic action can we explain the jaundice which develops in a twenty-year-old syphilis after a course of ten or twelve injections of arsphenamin. McDonald[204] reports five cases of acute yellow atrophy with necropsy following arsphenamin. In all five cases there was a microbic infection of a special type. He regards the infection as being the deciding factor with arsphenamin, mercury and previous damage as added factors. Friedmann[205] states that 3 per cent. of 511 cases had jaundice after neo-arsphenamin, and that further treatment was not injurious.

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[199] Stokes: J. A. M. A. **72**:241 (Jan. 25) 1919.

[200] Milian: Bull. et mém. Soc. méd. d. hôp de Par. **43**:821 (Oct. 17) 1919; abstr., J. A. M. A. **73**:1859 (Dec. 13) 1919.

Scott and Pearson[206] review the literature of case reports, necropsies and opinions concerning the relation of arsphenamin and jaundice in early syphilis. They advance a classification and report cases to fit the various classes. It would appear from this paper that jaundice does not occur in early syphilis as a result of arsphenamin treatment unless the liver has already been damaged. The associated liver damage is chiefly due to syphilis, but may be due to alcohol. The jaundice due to the combined action of syphilis and arsphenamin is not obstructive, but is characterized by diffuse degeneration of liver cells.

REACTIONS IN RELATION TO THE SKIN

Zieler[207] asserts that melanoses and hyperkeratoses occur very rarely after arsphenamin. He believes at least in his own cases, that the trouble was produced by mercury rather than by arsenic, and that it was seen most often when arsphenamin was given along with mercury. Heller[208] answers Zieler's discussion and defends the view that arsenic keratosis is more common than mercurial.

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[201] Sicard, Haguenan and Kudelski: Bull. et mém. Soc. méd. d. hôp. de Par. **43**:880 (Oct. 24) 1919; abstr., J. A. M. A. **73**:1965 (Dec. 27) 1919.

[202] Giroux: Bull. méd. **33**:739 (Dec. 6) 1919; abstr., J. A. M. A. **74**:425 (Feb. 7) 1920.

[203] Chabrol and Khoury: Paris méd. **9**:467 (Dec. 3) 1919; abstr., J. A. M. A. **74**:360 (Jan. 31) 1920.

[204] McDonald: Brit. M. J. **1**:76 (Jan. 19) 1918.

[205] Friedmann: Dermat. Ztschr. (Dec.) 1918; abstr., Berl. klin. Wchnschr. **56**:209 (March 3) 1919.

[206] Scott and Pearson: Am. J. Syphilis **3**:628 (Oct.) 1919.

[207] Zieler: Berl. klin. Wchnschr. **56**:346 (April 14) 1919.

OTHER COMPLICATIONS OCCURRING AFTER ARSPHENAMIN

Variot and Bouquier[209] report the occurrence of polyneuritis in a nonsyphilitic 13-year-old child following treatment by arsphenamin. Sutter[210] reports a case of gangrene in the fingers with anesthesia of the forearm, apparently the effect of the leakage of arsphenamin solution outside of a vein at the elbow. Schwerdtfeger and Tinker[211] report the occcurrence of pneumonia in each of nine patients injected with the same solution. All had an immediate reaction. The authors attribute the reaction to the drug, but the evidence submitted by them and by Schamberg in comment on this report in the article which follows theirs shows that it was not the drug, but probably the concentration, speed of injection and possibly the reaction of the solution. Goldberg[212] reports a case of injury to the median nerve by paravenous arsphenamin injection.

THE CURE OF SYPHILIS

Opinions as to the possibility of the cure of syphilis are divided. Warthin[213] states that our present day treatment seems only to succeed in rendering the infection latent rather than in curing it. He bases this statement on the finding of persisting active lesions and spirochetes in tissues of syphilitics whose disease was clinically inactive or "cured." Clinicians, on the whole, are more hopeful. Reinfection has been assumed to be evidence of the cure of the first infection. A fairly large number of case reports of reinfection have been published. Schamberg[214] has recently reported one case, Goulart[215] three, and White[216] twenty-eight cases. Gibson[217] has not seen a case of secondary syphilis, which gave a negative reaction for six months after treatment with arsphenamin and mercury was discontinued, again develop a positive blood test unless reinfected. It is the opinion of Pinard[218] and of many others that absolute eradication of the disease seems possible when treated in the early stages.

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208. Heller: Berl. klin. Wchnschr. **56**:542 (June 9) 1919.
209. Variot and Bouquier: Brit. J. Child. Dis. **16**:4 (Jan.-March) 1918.
210. Sutter: J. A. M. A. **73**:1611 (Nov. 22) 1919.
211. Schwerdtfeger and Tinker: Am. J. Syphilis **3**:398 (July) 1919.
212. Goldberg: Berl. klin. Wchnschr. **56**:609 (June 30) 1919.
213. Warthin: Am. J. M. Sc. **152**:508 (Oct.) 1916.
214. Schamberg: J. A .M. A. **73**:826 (Sept. 13) 1919.
215. Goulart: Arch. Brasil de med. **9**:138 (March) 1919; abstr., J. A. M. A. **73**:728 (Aug. 30) 1919.
216. White: Brit. M J. **2**:509 (Oct. 20) 1917.
217. Gibson: Brit. M. J. **1**:151 (Feb. 8) 1919.
218. Pinard: Presse méd. **27**:249 (May 8) 1919.

The criteria of cure are stated by Dinnick[219] as follows: If after an intensive course of arsenical medication and the continuous exhibition of mercury for two years a patient can show two years of freedom from physical signs of the disease, has a persistently negative blood serum, a cerebrospinal fluid which shows no variation from the normal, either in pressure, globulin content or cellular count and which gives a negative Wassermann reaction in amounts of 2 c.c.; and if after a period of freedom from treatment these conditions are still present and persist in spite of provocative treatment, it is justifiable in our present state of knowledge to presume that the patient is cured.

LeComte[220] states that the criteria for cure today include treatment with arsphenamin and mercury until negative blood findings are secured and treatment with mercury for at least six months after this; observation for eighteen months after this with frequent negative blood examinations followed by negative cerebrospinal fluid findings. Any relapse should be considered as a reinfection as far as cure is concerned. Even with this it is scarcely possible to assure the patient that he is cured beyond doubt. He should be told of his chances for cure and told to report at yearly intervals in the absence of any further symptoms for further examinations.

Wile and Hasley[221] point out that the serologic and clinical cure are not necessarily parallel. With the ever increasing discrepancies reported with each refinement of the Wassermann test and with the ever increasing number of permanently positive cases previously regarded negative, it appears that as a guide to therapeusis the Wassermann reaction is absolutely unreliable.

According to Buschke,[222] tabes and paresis cannot assuredly be prevented in spite of the abortive treatment of primary syphilis. He has noted cases with no secondary symptoms and a negative Wassermann reaction for from two to three years in which new symptoms developed.

The outlook is surely not so dark as some of these observers have painted it. It is the opinion of many syphilographers, based on a large experience, that syphilis may be cured permanently by the methods now in use. The earlier in the disease the treatment is begun, the larger the percentage of apparent cures.

The possibilities of cure in hereditary syphilis parallel those discussed above in regard to acquired syphilis. Negative serology is obtained with the same ease when the treatment is carried out along

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219. Dinnick: Lancet **1**:1055 (June 21) 1919.
220. LeComte: Am. J. Syphilis **3**:106 (Jan.) 1919.
221. Wile and Hasley: J. A. M. A. **72**:1526 (May 24) 1919.
222. Buschke: Therap. d. Gegenwart. **60**:7 (Jan.) 1919.

modern lines, and clinical cure is just as frequent. Adams[223] obtained a negative reaction in the child more quickly than in the mother, and he found that in nearly all syphilitic children born alive, treatment can convert a positive Wassermann reaction to a negative, and that the children become healthy and show regular gains in weight.

Müller and Singer[224] review their experience since 1909 when the first Welander home for children with inherited syphilis was inaugurated in Germany. They claimed that far better results have been realized by this prolonged systematic treatment than by any other means. Though a final judgment is possible only when the patients become thirty, forty, or more years of age, it is already evident that most serious consequences can essentially be attenuated or even the complete cure of the patient be accomplished. The children were given from seven to nine courses of treatment over a period of three to four years.

After discharge from the Home, eighty-four children were followed. Of sixty-nine children followed to date, all had a negative Wassermann when last seen. Of these, 74 per cent. had a normal mentality and 9.5 per cent. were socially useless because of mental defect. The mortality among 281 syphilitic infants was 35 per cent.

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[223] Adams: Brit. M. J. **2**:541 (Nov. 16) 1918.

[224] Müller and Singer: Arch. f. Kinderh. **67**:161 (May 17) 1919.

The American Medical Association will pay thirty cents each for the following issues of the AMERICAN JOURNAL OF DISEASES OF CHILDREN: January, 1913; February, March, November and December, 1914; January and August, 1915; January, 1918; March and April, 1919. Address to AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Ill.

American Journal of Diseases of Children

Vol. 20 SEPTEMBER, 1920 No. 3

THE SIGNIFICANCE OF XANTHOCHROMIA OF THE CEREBROSPINAL FLUID

WITH REPORT OF A CASE IN A PREMATURE INFANT*

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This case is reported because of the occurrence of yellow spinal and ventricular fluid in an infant of eight months period of gestation who lived thirty-seven days and who also manifested marked internal hydrocephalus, pyelitis and bronchopneumonia. In the literature the term xanthochromia covers a variety of cerebrospinal fluids with different properties. Some insist that this name should be applied to yellow fluids which coagulate *en masse,* as Froin first described. Others reject the term xanthochromia when applied to fluids containing red blood cells. They propose the term erythrochromia for this condition. Our case was one of yellow cerebrospinal fluid containing red cells due to subpial hemorrhages. Because of the confusion and lack of agreement concerning our chief interest in this case, we will be obliged to interpret our conception of the condition called xanthochromia in order to present intelligently the findings.

The common properties of all xanthochromic fluids are yellow color and increased globulins. After these have been eliminated, the other considerations such as massive coagulation, pellicle formation, cell count and the presence of erythrocytes, are variable factors. The syndrome of xanthochromia most frequently mentioned is Froin's, or the complete syndrome which includes yellow color, massive coagulation and increased globulins. The cell count varies. Some include and others disregard the cells in their discussions because they have not analyzed their significance. It seems unnecessary to mention increased globulins where coagulation occurs, because coagulation without an increase in albumen is inconceivable. As a matter of fact, fluids with xanthochromia all have increased globulins, although the quantity may differ. Nonne has described what is now termed the incomplete syndrome, that is, yellow color with increased globulins, although massive coagulation does not occur. There seems to be considerable evidence, as we shall see later, that Nonne's is an earlier or less complete development of Froin's syndrome. In general, it has been pointed out that the French emphasize the coagulation feature, while the German school speaks of the increased globulins, not mentioning the presence or absence of coagulation.

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* Read before the American Pediatric Society, Highland Park, Ill., May 31, June 1 and 2, 1920.

The whole situation resolves itself into the question of what causes the yellow color. Ultimately, the yellow pigment is hematogenous in origin. Mix[1] states that the pigment has been identified as hemolytic biliary pigment by Donath, as bilirubin by Blanchetriére and Lejonne, and as urobilin by Fornaca. Raven suggests that the color, in the last analysis, is due to blood pigment from multiple small hemorrhages because in his 47 cases, the yellow color was caused by an old hemorrhage. His conclusions hold only so far as those cases are concerned. Other causes must be assigned where no demonstrable hemorrhage is present. However, his opinion is confirmed by the case of Blanchetriére and Lejonne, a vascular cord tumor with multiple hemorrhagic foci. There were only a few red cells in the fluid, and they suggest that there were small continuous hemorrhages from the tumor over a period of sixteen months. All these cases might be classed as erythrochromic so far as the presence of red cells is concerned. There are other views concerning the pigment which refer particularly to the other types of xanthochromic production. Gordon[2] remarks that the pigments accumulate in greater concentration where there is a limited area for absorption as in a culdesac or in the cutting off of the spinal subarachnoid space in hydrocephalus. Inasmuch as absorption from the spinal subarachnoid space is all by way of the blood stream, and this course is closed by compressions and inflammations, as in the complete syndrome of xanthochromia, the pigment will have to accumulate in the meningeal pouch so formed. Thus, Raven, on the one hand, explains the yellow color on the basis of hemorrhage entirely, and Gordon, on the other, takes into account only the compression syndrome. Both are xanthochromic fluids, although the former may be termed erythrochromic and the latter the true Froin syndrome with the absence of red cells.

Instead of considering the other properties of xanthochromic fluids separately, we shall find that they can all be explained in a discussion of the pathogenesis of yellow color itself. This will simplify the problem and permit a more lucid presentation of the subject itself. The most usual form of xanthochromia is that associated with compression of the spinal cord. Since first described in 1903, a large number of cases have been reported in the literature. Derrien, Mestrezat[3] and Rogers claim they were the first to point out the importance of the formation of a meningeal pouch in the production of xanthochromia. Siccard and Descomps were among the first to call attention to this fact, although they were wrong in their idea that the syndrome always spelled meningitis and never tumor. Indeed, since their time, most of the cases reported are cases of tumor. Everyone who has written on the subject has agreed to the importance of the pouch formation, and only recently Ayer[4] published some experimental work on the production of xanthochromia by compression produced by injecting paraffin into the spinal canal.

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[1] Mix: Surg. Clin. **4**:317, 1915.
[2] Gordon: Canad. M. A. J. **9**:1005, 1919.

The obstruction may be produced by tumor, meningeal adhesions and trauma. The tumors may be of the ball-valve type, as Mix points out, and this will explain the variability of fluid findings which occur in some cases. Mestrezat showed that a transudate occurs into the meningeal pouch. In a closed cavity of this sort the elements necessary for xanthochromia and massive coagulation could come in two ways, as Horrax[5] states, either by transudation or by capillary hemorrhage the origin of which is not so clear although a few cases are reported with cord tumors. Mestrezat concludes that the physical and chemical properties of the fluid, together with the clinical and necropsy findings, demonstrate that a closed cavity and stasis of the fluid is necessary to the production of the syndrome. Therefore, there must be a closed cavity in which there accumulate the elements from the blood by transudation or hemorrhage, and, second, an alteration in the vessel walls of the cavity, either infectious or toxic, permitting the process to occur. It is usually a transudate. There is diminished pressure in the culdesac because the spinal fluid above the compression is shut off. The veins are dilated at the compression so that it is easy for transudation to occur. There is a high albumin content, and thrombin and fibrinogen also pass out. Mix states that these are the most characteristic constituents. Coagulation may occur in the needle itself, but sometimes it takes as long as a few hours to occur. The clot separates out from the fluid as a blood clot behaves. He points out that the fibrin content runs close to the amounts found in the blood. Hanes[6] states that the high content of xanthochromic fluids in fibrin and proteids and the presence of a few cells support the view that real blood comes with the transudate, which is perfectly analogous to pleural transudates due to venous compression.

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[3] Mestrezat: Thesis Paris, p. 425, 1912.

[4] Ayer: Arch. Neurol. & Psychiat. **2**:158 (Aug.) 1919.

[5] Horrax: Arch. Int. Med. **17**:632 (June) 1916.

What determines the presence or absence of cells and what is their significance? Although we discussed the compression from the standpoint of the tumor, it is readily seen that the same symptoms might be produced by an inflammatory mass or traumatic process. In these cases the cell count is increased. Indeed, some authors suggest that an increased cell count differentiates tumor from inflammatory processes. Sprunt and Walker,[7] however, show that in seventeen of fifty-one cases of tumor the cell count was increased, and in one of their cases, a cord tumor, there were 61 mononuclear cells.

The formation of a pellicle is to be expected where there is a meningitis with insufficient compression to cause massive coagulation. It may also occur in the early stage of a tumor. Cooper[8] describes a case of angiosarcoma of the cord which showed edema of the membrane below the point of construction from which yellow fluid was withdrawn. A cobweb-like coagulum formed when the fluid was allowed to stand. There were no cells, and the globulins were increased.

The total absence of coagulation may also be explained. In the compression type of case it is a matter of duration of the process and the completeness and extent of the compression. Ayer[9] states that the most important variation gives a fluid which superficially does not seem to have any relation to the complete syndrome. Where presumably the pressure on the cord has been insufficient to shut off the spinal fluid we find a fluid of normal appearance, colorless, under normal pressure, but containing an abundance of globulins. This fluid does not clot and may not contain cells. Such a fluid corresponds more closely to Nonne's incomplete syndrome. As a variation from this the yellow color may be present. Hanes attempts to prove that Nonne's is only an earlier stage of the same process that gives Froin's syndrome. However, it may as well be a question of extent of obstruction as duration. Hanes states that the complete syndrome may never be reached, but that the yellow color, increase in proteins and cells may be the only evidence of cord compression. What has been said regarding cell increase should be recalled here. Nammack[10] recently reported his observations on 5,801 spinal punctures. He quotes the ninety-two cases of tumors and other chronic surgical conditions of the cord by Elsberg and Rochefort[11] in which there were twelve fluids with xanthochromia, seven of which gave the complete syndrome. Of his own cases there were ninety-six, or 1.6 per cent., of yellow spinal fluids. In only six of his cases was the complete syndrome found. Yellow fluids occurred in two-thirds of his cases of tuberculous meningitis. He concludes that the smaller incidence of the complete syndrome in his cases was another indication that the earlier stages showed the Nonne syndrome, inasmuch as all his cases were acute or subacute affections. Incidentally, he remarks that a patient with meningeal symptoms and yellow fluid should be suspected of either tuberculosis or poliomyelitis. It may not be quite fair to include such cases of Nammack's with causes of cord compression because in the infections the factor of hemorrhage may play an important part. Blood cells are frequently found in tuberculous meningitis, and it is questionable whether hemorrhage alone gives the complete syndrome. The question of hemorrhage and its relation to xanthochromia we will consider separately. So far we have described the formation of yellow color, bringing in the explanations for massive coagulation, pellicle formation, cell increase and absence of coagulation.

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[7] Sprunt and Walker: Johns Hopkins Hosp. Bull. **28**:80, 1917.

[8] Cooper: J. A. M. A. **55**:2298 (Dec. 30) 1910.

[9] Ayer: Med. Clin. **1**:1143 (Jan.) 1918.

[10] Nammack: Am. J. M. Sc. **159**:540, 1920.

[11] Elsberg and Rochefort: J. A. M. A. **68**:1802 (June 16) 1917.

The second type of process which gives xanthochromia without demonstrable compression phenomena is the process of continuous or multiple capillary hemorrhages. The compression phenomenon applied particularly to cord processes, although in Hane's case of a 9 months old child a tuberculous mass obliterated the pia arachnoid and completely encased the medulla at the level of the foramen magnum. The ventricular fluid was clear, but the spinal fluid presented the complete Froin's syndrome. The group we will now consider includes those cases of inflammation, neoplasms and trauma associated with red cells in the cerebrospinal fluid. The color of the fluids is due to dissolved hemoglobin or its derivatives, and they do not coagulate, as a rule. Because of the presence of erythrocytes some propose the name erythrochromia and place them in a separate category.

There are many cases in the literature illustrating the occurrence of yellow spinal fluid with conditions permitting the slow escape of blood. In 1904, Cestan and Ravaut published a case of pachymeningomyelitis of the conus. They considered two factors in the production of the complete syndrome, first, a meningeal inflammation with a sero-fibrinous exudate and, second, hemorrhage with solution of the red cells in the fluid with the appearance of the yellow color due to freeing of the hemoglobin. These two factors may coexist. In fact, Babinski regarded the syndrome of Froin as being due to a fibrinous hemorrhagic meningitis.

Another type of process recalls the case of Blanchetriére and Lejonne to which reference has already been made. This was a vascular cord tumor of the small round cell type which contained many hemorrhagic foci. There were only a few cells in the fluid, and they accounted for the yellow color on the hypothesis that small continuous hemorrhages had occurred over a period of sixteen months. In Raven's forty-seven cases the spinal fluid was stained by the hemoglobin derivatives from old hemorrhages. Rindfleisch, in 1904, had three cases of metastatic sarcoma of the brain and cord. In two the fluid was once dark golden brown while at another time the fluid was clear yellow. This expresses well the relation of erythrochromia to xanthochromia, if such a distinction is desired. The sediment contained erythrocytes and large cells with large nuclei, probably endothelial cells, and the proteins were increased. Section of the tumor showed hemorrhagic foci. Dufour, in 1905, described a case of diffuse sarcomatous meningitis with yellow fluid containing many lymphocytes, a few erythrocytes and several makrocytes. He states there was no bleeding in this case. Not all blood containing tumors give rise to red cells in the fluid. In 1906, Grund described a case of gliosarcoma of the spinal cord with yellow fluid but no cellular elements. The spectroscope showed no blood although the tumor was full of the blood and extended to the meninges. In 1907, Erb reported a case of carcinoma of the cervical vertebrae with yellow fluid but no blood. In 1911, Heilig reported cases of "erythrocyte pigmentation" of the spinal fluid.

Tuberculous meningitis often, if not usually, shows red cells in the spinal fluid when associated with xanthochromia. Reich[12] described a case of tuberculous meningitis in which the fluid was of a light bloody color but became a golden brown after centrifuging. In the sediment there were many erythrocytes, lymphocytes and an occasional polymorphonuclear leukocyte. Necropsy showed a hemorrhagic condition. He concludes that not only in tumors, but in cerebral hemorrhagic conditions yellow color of the spinal fluid may be found.

Xanthochromia with red cells is not limited to the conditions so far discussed, namely, Babinski's type of fibrinous hemorrhagic meningitis, cord tumors and meningitis of tuberculous and purulent origin. There is a wealth of evidence pointing to the responsibility of conditions within the cranial cavity in the production of the combination of yellow color and red cells. Tuffier reports cases of yellow fluid in skull fractures. Another case is cited of a patient who was ready to be operated on for brain tumor. The patient died, and at the necropsy a diffuse cerebral hemorrhage was found. In one of Rindfleisch's cases a brownish blood coagulum was seen in the fluid, and in this case there was a tumor mass adherent to the inner side of the lateral ventricle. In one of Erb's cases there was a hemorrhagic glioma on the right side of the brain. In this case, the first puncture yielded a clear fluid, but the second puncture showed red cells, polynuclear leukocytes and lymphocytes. These characteristics continued for some time. Further evidence of the cranial origin of the hemorrhage is furnished by Horrax's case. He reports the case of a boy aged 12 years, with a tumor of the pineal gland. The spinal fluid was straw colored, cloudy, and contained 1,011 old, disintegrating red cells and eighty-five white cells. There was no massive coagulation although the globulins were increased. From the ventricle of the same case 50 c.c. of yellow fluid with 561 old red cells and seventeen lymphocytes was obtained. Horrax states that many tumors grow into the ventricles accompanied by xanthochromia doubtless due to the escape of red cells from the surface of the tumor into the fluid. He reports having seen a number of such cases in his clinic. Sprunt and Walker hold that it is generally recognized that yellow color may occur in the spinal fluid after ventricular hemorrhage or hemorrhage into the subarachnoid space when the cells have disappeared almost entirely. They reviewed 100 cases from the literature and stated that there are some exceptions to the syndrome that cannot be explained on the basis of compression and obstruction. These usually vary from the complete syndrome in some particulars. Among the cases unexplainable on the theory of compression is a group of brain tumors in contact with the meninges in which the yellow color and other abnormalities could be explained by small hemorrhages into the subarachnoid space. In these cases, they state, there are crenated blood cells or positive tests for hemoglobin. To the number of cases we have already quoted in support of this view, they add a case of endothelioma of the dura in the left middle fossa and a case of arteriosclerosis, chronic diffuse nephritis and arterial hypertension with hemorrhage into the lateral ventricles.

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[12] Reich: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **25**:721, 1913.

Hanes attaches considerable importance to the condition he calls erythrochromia and sharply distinguishes this from xanthochromia. According to him, the name erythrochromia would have to be applied to any xanthochromic fluid containing red cells. This would necessitate a division of yellow fluids which would hardly be justified on etiologic or pathologic grounds as the cases we have described would indicate. We do not wish unduly to emphasize the hemorrhage factor and we are inclined to agree with Sprunt and Walker that it is not necesary to presuppose minute hemorrhages to explain the color of the fluids in which there are no red cells and in which the most delicate tests for hemoglobin derivatives are negative and no bands appear in the spectrum. From the large amounts of fibrin and globulin it is evident that considerable transudation of blood plasma must have occurred. However, we think that certain conditions associated with hemorrhage have a definite place in the causation of xanthochromic fluids and cannot agree to a separation simply on the presence or absence of red cells. Essentially, the same process and origin of yellow fluid exists in both types. The process may better be understood if the whole question is simplified by classifying the conditions producing xanthochromia rather than to separate the syndrome on the grounds of more or less accidental variations in the fluid.

Hanes states that erythrochromic fluids are due to hemorrhage into the cerebrospinal fluid from ventricular apoplexy and traumatic rupture of meningeal vessels. We have already referred to cases of brain and cord tumors and cases of fibrinous and tuberculous meningitis giving red cells. He says that the color varies from bright red to a dark yellow and changes from day to day. Sprunt and Walker also state that in their experience the fluids containing hemoglobin are dark and have an amber tint, whereas those giving negative tests are of a lighter buff yellow. However, one of Froin's cases varied from cherry red to red, reddish yellow, light yellow to absolute limpidity. Nine punctures were made from the first to the twenty-first day of the illness. The red cells were present in diminishing numbers, and serum albumin and globulin were present in varying amounts. The spectroscopic evidence of hemoglobin disappeared some time before the fluid became colorless.

A case cited by Siccard and Descomps showed red cells in the serum and in the clot that formed almost immediately in a xanthochromic fluid. A second puncture six days later was yellow and clear, and a third, twenty-three days after the first, was entirely clear.

The mere presence of red cells does not take the fluid out of the category of xanthochromia where the fluid is really yellow. In fact, the red color, although not a genuine xanthochromia, may precede the yellow color in point of time and probably is due to continuous hemorrhage. Gordon agrees with this conception, for he states that in many cases of xanthochromia there are either free red cells or the evidence of chemical blood. In others there is no chemical evidence of hemoglobin, but he concludes, as we have already mentioned, that there is no evidence that the pigment is other than the normal pigment of the blood plasma. In this connection let us again recall Rindfleisch's two cases of metastatic sarcoma of the brain and cord. The fluid in these cases was once dark golden brown while at another time it became clear yellow.

Hanes points out that another differentiating point is the constancy of the color in xanthochromia, but Siccard and Descomps have described the presence of xanthochromia and massive coagulation on some punctures and not on others. In Dimolet's [13] case, the first flow of yellow color actually changed to normal during the course of a single puncture. Sprunt and Walker cite a case in which a second puncture, performed three weeks after the first, yielded a clear yellow fluid with very faint globulin tests, and this at a time when the symptoms of compression were more marked.

The fluid may have the color of arterial blood and red cells or their shadows are found. In the minute type of hemorrhage, there will be no red color at all, and red cells have been found in fluids which were decidedly yellow and not contaminated with blood macroscopically.

Another objection to the red cells is based on the statement that leukocytosis of the fluid develops because of the meningeal irritation by the products of red cell destruction. However, in Horrax's case the ventricular fluid contained 561 red cells and seventeen lymphocytes. More white cells and more varieties should be expected. It is not denied that leukocytosis may occur, as in the case of Schwartz that Hanes quotes in his contention, but this is not a constant or characteristic part of the hemorrhage. It may be due to the infection producing the meningitis.

The fact that xanthochromia shows no red cells, and that there is neither chemical or microscopic evidence of hemoglobin derivatives is contradicted by Froin's first case, in which red cells were present, and Reichmann's report that he has often found the syndrome in cases of tumor of the brain and cord with yellow spinal fluid and multiple hemorrhages.

REPORT OF CASE

Our case belongs to the second type of yellow fluids, that is, the type not associated with compression but occurring with a process allowing blood to escape into the cerebrospinal fluid.

The infant was a premature baby, born during the eighth month of gestation. The mother had influenza and pneumonia. The child was brought to the hospital as a feeding case. The admission history stated that the child was apparently well at birth and the labor was not difficult. The father was well. Two maternal aunts had tuberculosis, and one died of the disease. The mother of the baby had frequent attacks of bronchitis, but the family physician stated that the process was not tuberculous.

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[13] Dimolet: Rev. Neurol. **22**:648, 1914.

On entrance the temperature was 95 F., and the child weighed 3 pounds 14 ounces. The child was placed in an incubator, and the temperature rose to 98.6 F. the next day. Breast milk was given by gavage, and occasionally skimmed milk was given during the stay of thirty-four days. The weight steadily increased to 5 pounds 2 ounces. After a few days of subnormal to normal temperature, it tended to rise so that it frequently reached 102 F. during the first ten days of life. This was not deemed particularly remarkable in view of the prematurity with its unstable heat regulating mechanism.

On the twelfth day of life, the baby vomited two of its feedings. The vomitus was streaked dark brownish. The next day the baby vomited three times, and some separation of the cranial sutures was noted. This finding was not considered unusual because premature babies frequently show signs of hydrocephalus. The same evening twitchings of the entire body were observed. On the fourteenth day the temperature rose to 106 F. There were marked convulsions and spasticity. These symptoms continued until the end. There was an occasional râle in the right axillary region. The vomitus was dark brown, but the Weber test for blood was negative. The infant was catheterized, and only a few drops of urine was obtained. There were many leukocytes, some of which were in clumps, many granular casts, some of which were particularly large, and amorphous urates. No red cells were found. Subsequent urinalysis showed traces of albumin, reducing substance, acetone and granular casts, which diminished in number so that the last two specimens, on the twenty-first and thirty-second days, were free. Leukocytes persisted in the urine often clumped, and there were occasional red cells and epithelial cells. The cultures from the urine showed gram-negative bacilli and gram-positive cocci. There was no blood in the stool. A vaginal smear was negative; throat culture was negative; an eye smear taken from the discharge one day before death contained many leukocytes and a few cocci which were not morphologically gonococci.

The temperature tended to maintain itself between 99 and 102 F. for the rest of the time, although it was subnormal for the four days before death. On the twentieth day fine râles were heard in an area 4 cm. in diameter over the anterior surface of the left lung. They were heard at the end of deep inspiration after crying. Râles were also heard over the left upper lobe posteriorly. There were occasional râles over the right lung. The breath sounds were more distinct and sharper on the left side. Evidence of fine bronchitis persisted to the end.

On the twenty-fifth day two sharply demarcated, ulcerated areas appeared on the buttocks in symmetrical arrangement. That day the temperature was 104 F. The extremities were contracted and spastic. The diagnosis of meningeal hemorrhage was suggested. On the thirtieth day, in addition to the general spasticity, there was a sharp cephalic cry, and the anterior fontanel was bulging.

Spinal puncture yielded 4 c.c. of yellow fluid which appeared clear and in color resembled picric solution. A filmy pellicle separated out from the first tube in about five minutes. This tube contained the first 2 c.c. of fluid. There were 962 cells, most of which were polymorphonuclears. There were some red cells in the spinal fluid, but they were dissolved in acetic acid before the count was made. Therefore, some, at least, of these leukocytes came from the blood. Although massive coagulation did not occur, the expected large increase in globulins was proved by the Nonne, Ross Jones, Noguchi and Pandy tests, all of which gave heavy precipitates. Smears of the pellicle showed large numbers of polymorphonuclear leukocytes, considerable fibrin but no organisms by methylene blue, Gram or acid fast stains. The colloidal gold test showed reduction in the meningitic zone. The fluid was interpreted as indicating old blood in the cerebrospinal fluid. This would account for the yellow color, large quantities of globulin and cells. The predominance of white cells was accounted for on the theory that solution of red cells had occurred, leaving white cells and yellow color. The increase in polymorphonuclear cells would be explained on the increased polymorphonuclear content in the blood of the infant who also had a pyelitis and bronchopneumonia. This was probably the correct interpretation because the meningitis found on microscopic examination gave rise to round cell infiltration rather than polymorphonuclear cells.

On the thirty-first day, the spasticity of the extremities was still marked. On the thirty-second day the left lateral ventricle was punctured. Twenty c.c. of deep yellow fluid was obtained under greatly increased pressure. Following the puncture, the child became quiet, vomited and the bulging of the fontanel diminished. There were ninety-one cells, of which 78 per cent. were polymorphonuclears, 16 per cent. lymphocytes and 6 per cent. endothelial cells. There were also red cells, and the benzidin test was positive. The globulins were increased, although not to the same degree that they were found in the spinal fluid. The ventricular fluid showed reducing substance. No bacteria were seen on smear, and in the cultures of both spinal and ventricular fluids there were no organisms. The Wassermann tests on both fluids were negative. The child died on the thirty-seventh day.

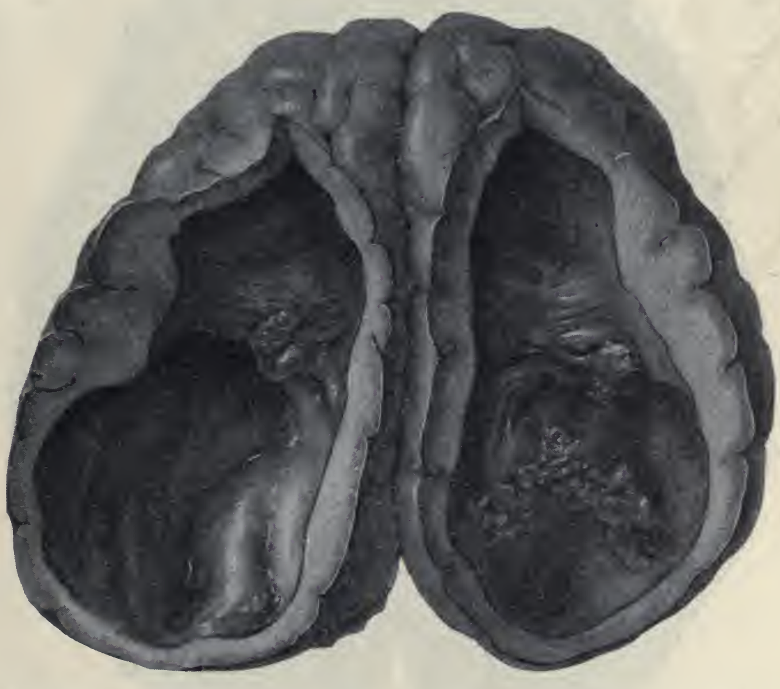

Fig. 1.—Lateral ventricles exposed, showing dilatation and exudate and enlarged choroid plexus. Exudate was pale yellow.

The necropsy was performed seven and one-half hours after death by Dr. Oscar Schultz. The fontanels were open and protuberant. When the dura was incised, considerable yellow fluid escaped. The inferior surface of the brain was yellow and was covered in areas by a layer of soft, pale yellow exudate between which the pia appeared congested and thickened. The lateral ventricles were distended and contained a slightly cloudy yellow fluid. The fluid of the right lateral ventricle was darker than that of the left, but there was no brownish tinge. There were loosely adherent masses of opaque, yellowish white, soft material on the floor of the right ventricle. The right choroid was transformed into a soft red fleshy mass 2.5 cm. long and 0.6 cm. wide. The fourth ventricle was greatly distended. The dura of the cord was normal. The outer surfaces of the pia anteriorly had a yellowish tinge, and in the thoracic region the pia was thickened by a layer of grayish white material between pia and cord. Smears from the ventricular fluid and from the fibrinous material of the right ventricle contained no bacteria. In cultures from these sources a very small number of staphylococcus colonies developed.

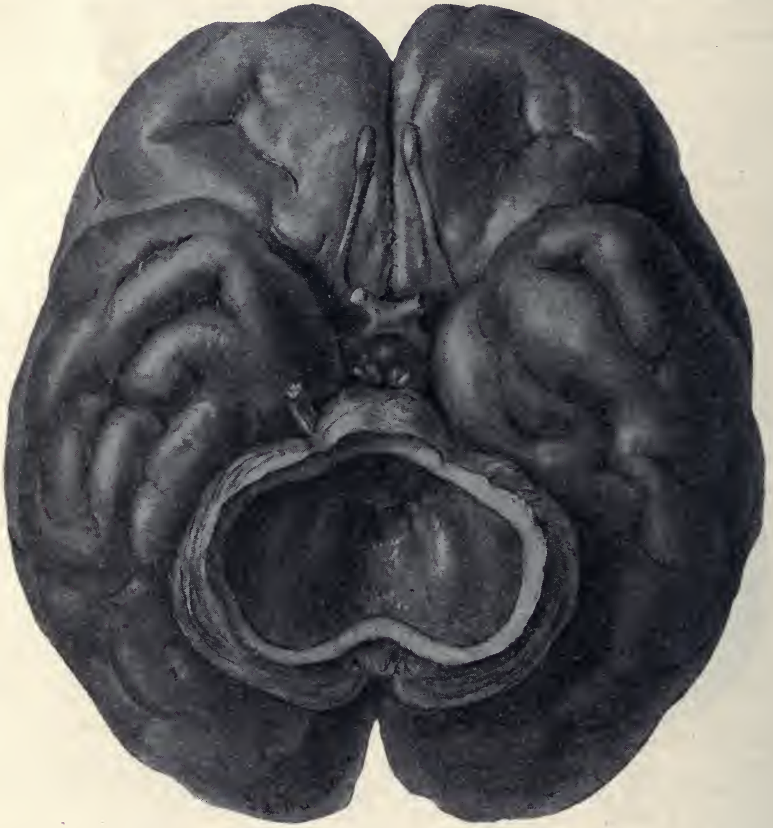

Fig. 2.—Fourth ventricle, showing dilatation.

Microscopic examination by George B. Hassin revealed a marked perivascular infiltration with lymphocytes and plasma cells, and marked vascular proliferation diffusely over the brain and cord. There were parenchymatous changes in the ganglion cells and proliferation of the glia. The markings between the gray and white substance were totally obliterated. There were areas of softening in the deeper layers of the white matter crowded with fat granular bodies. In one area a clump of bacilli was seen. The pia was markedly infiltrated with lymphocytes and plasma cells. There were numerous hemorrhagic foci. Throughout the specimen there were many microphages packed with hemoglobin and red cells. Careful microscopic examination ruled against the diagnosis of tuberculosis, although the original impression of a tuberculous lesion might have been made from a gross examination of the surface. He concluded that this was a case of meningo-encephalitis of some infectious origin and that the xanthochromia was undoubtedly due to numerous subpial hemorrhages.

The rest of the necropsy findings may be summarized briefly: The body was that of a poorly nourished white female 45 cm. long. There was very little subcutaneous fat. The serous cavities were normal. The foramen ovale was open to the extent of 2 mm. in diameter, otherwise the heart was normal. Both lungs were congested posteriorly, and the posterior portion of the right lung was firmer than the rest of the tissue. On section this was red, had a fleshy appearance and contained little air. The abdominal organs were apparently normal. Microscopic examination showed that the heart was negative. In sections from the posterior portions of the lungs, the bronchi were filled with polymorphonuclear cells, and in some of them the epithelium was desquamated. The septal vessels were distended, and the alveoli were filled with polymorphonuclear leukocytes. In one lung the consolidation was diffuse and widespread. In the other the areas of consolidation occurred about the bronchi, and air containing alveoli were present between the consolidated areas. In the anterior portions of the lung the septa were thicker than normal, due apparently to incomplete expansion. The lymphoid tissue of the spleen was small in amount. The tissue was greatly congested. The liver cells were moderately swollen. The pelvis of the kidney showed the subepithelial stroma diffusely infiltrated by lymphocytes, plasma cells and eosinophils. In one kidney the pelvic epithelium was absent in an area of considerable size, and the adjacent tissue of the medulla was diffusely and richly infiltrated with polymorphonuclear leukocytes. The cortex showed no involvement. The ureter and bladder were negative. The vessels of the suprarenal medulla were distended. The anatomic diagnosis, therefore, includes bilateral acute hypostatic pneumonia, bilateral subacute pyelitis and unilateral acute pyelonephritis.

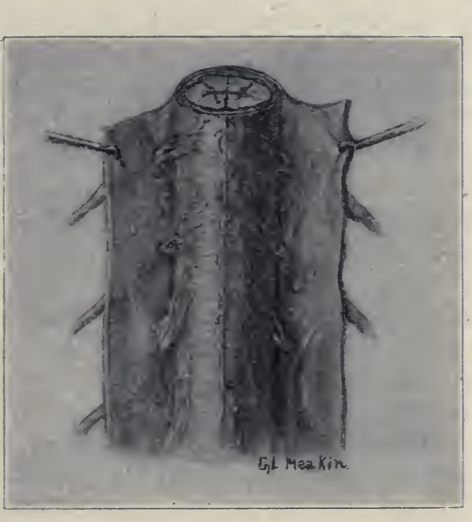

Fig. 3.—Cord showing fibrinous deposit. This was yellow colored.

We are not prepared to state the nature of the infection causing the meningo-encephalitis and subpial hemorrhages in our case, although the finding of a clump of bacilli in a necrotic area of the brain stimulates speculation. The only other case in the literature that corresponds to the findings of xanthochromia and red cells in the spinal and ventricular fluids present in our case is that of Horrax. This case, to which we have referred, occurred in a 12 year old boy from whom 40 c.c. of yellow spinal fluid was withdrawn which did not coagulate. It contained 1,011 old disintegrating red cells and eighty-five white cells. Fehling's solution was reduced; the Noguchi test was positive; and there were no tubercle bacilli. In our case the red cells were not counted, but there were 962 cells, most of which were polymorphonuclear. The ventricular fluid from Horrax's case, of which over 50 c.c. was withdrawn, contained 561 old red cells and seventeen lymphocytes. There was no massive coagulation, and Fehling's solution was reduced. We obtained 20 c.c. of fluid; the red cells were not counted. There were ninety-one white cells, 78 per cent. of which were polymorphonuclears, 16 per cent. lymphocytes and 6 per cent. endothelial cells. The benzidin test was positive, and reducing substance was present. The difference in cell findings is explained by the fact that the case of Horrax was one of pineal gland tumor while ours was a meningitis.

Other instances of ventricular puncture are noted but no xanthochromia. The cases of Leitch[14] and Hanes demonstrated that the ventricular fluid was clear while the spinal fluid was yellow, due to obstruction in the first case by tuberculous thickening and adhesions of the cervical membranes, and in the second to a tuberculous tumor blocking the pia-arachnoid at the level of the foramen magnum. The youngest case hitherto recorded was the case of Leitch, of tuberculous meningitis in a nine months old boy.

Our case belongs to the class of xanthochromic fluids without massive coagulation and with red cells. It might be termed a case of the incomplete xanthochromic syndrome containing red cells. This case may never have reached the complete stage. It is interesting to recall that Cestan and Ravaut stated in 1904, on the basis of their case of pachymeningomyletis of the conus that two factors may produce the syndrome of xanthochromia, coagulation *en masse* and increased cells. Although ours is not one of the complete syndrome, the factors stated by these authors are pertinent. One of the conditions they mention is a meningeal inflammation causing a serofibrinous exudate; the other is hemorrhage with solution of the red cells giving the yellow color to the fluid by freeing the hemoglobin. In our case both factors existed. This coexistence would tend to confirm Babinski's contention of a fibrinous hemorrhagic meningitis. However, this is only one of the conditions and not the most frequent, giving rise to yellow cerebrospinal fluid. Our case refutes the statement that in hemorrhagic meningitis the fluid is always red.

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[14] Leitch: Am. J. Dis. Child. **15**:348 (March) 1918.

Therefore, we report the case of an infant living thirty-seven days of eight months gestation with xanthochromia of the cerebrospinal fluid due to a meningo-encephalitis, with numerous subpial hemorrhages as the source of the coloration.

BODILY MECHANICS

ITS RELATION TO CYCLIC VOMITING AND OTHER OBSCURE INTESTINAL CONDITIONS

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The consideration of the mechanics of the body, especially those which affect the abdominal and thoracic organs, has received a new stimulus during the last few years. Life in the army during the war did a great deal to stimulate this interest. It showed that a great many men were physicially unfit and made a large number of men physically more fit. The medical men who were in charge of the unfit had an opportunity, in a large number of cases, to study and determine the cause of their unfitness.

When the results found in the army were compared with those of the draft boards, the conditions were found to be startling, not only from the point of view of the present generation but even more so for future generations.

An example of the importance of correct body mechanics is shown by some of the experiences of the first troops who went to France. In order to bring the regiments of the first division up to full war strength, many volunteers were accepted who were not given as careful a physical examination as the later draftees. About 800 or 900 of these men went out on a twenty-eight hour maneuver, five hours of which were spent lying down, and the following day 138 men were sent to the hospital for backache or trouble with their feet. All of these were found to have incorrect body mechanics.

The strain of military life in France was such that a very large percentage of the 15,000 men in the twenty-sixth division were unable to perform the work required of them, and consequently were unfit for active military duty. These men were also found to have very bad bodily mechanics. Since there were no transports to take them home, and the hospitals could not look after them, they were formed into a special training battalion. A course of education in bodily mechanics, or the proper use of their bodies, was given, and in six weeks time 80 per cent. were brought up to practically full physical efficiency. If these men had had a proper physical education before they went into the army an enormous amount of time, money and useless waste could have been avoided.

Very strict rules were consequently made by the government for the first examination of the draft boards, and out of 2,570,000 men between the ages of 21 and 31, examined by the draft boards, 29.1 per cent. were rejected on physical grounds. In other words, an army of 730,000 men were physically unfit for military service. In addition to this, when the men accepted by the draft boards were mobilized, about one quarter to one third were rejected by the military officers during the first year. This means that out of the original two and a half million draftees examined for the army 45 per cent. +, or nearly half, were rejected because of physical unfitness.

England overcame her shortage of man power during the late years of the war by taking those men who had formerly been considered unfit and bringing them up to full efficiency by a long course of training. The lack of proper education during the growing and formative periods of these men's lives not only cost the British Government a great deal of money but also much anxiety as to how to obtain the necessary man power.

In order to provide suitable education in bodily mechanics, one must understand what is good and what is bad bodily mechanics, and how to judge the same. Anatomists describe the normal human being and say there are fairly wide variations from the so-called normal. A superficial study of a large number of people will show that there are many varieties of human beings; some are relatively tall and thin, and no matter what they eat can never get fat; while others are relatively short and stocky and have a tendency to get fat no matter how little they eat. These two extremes show marked physical differences but despite this, both may be considered to be normal.

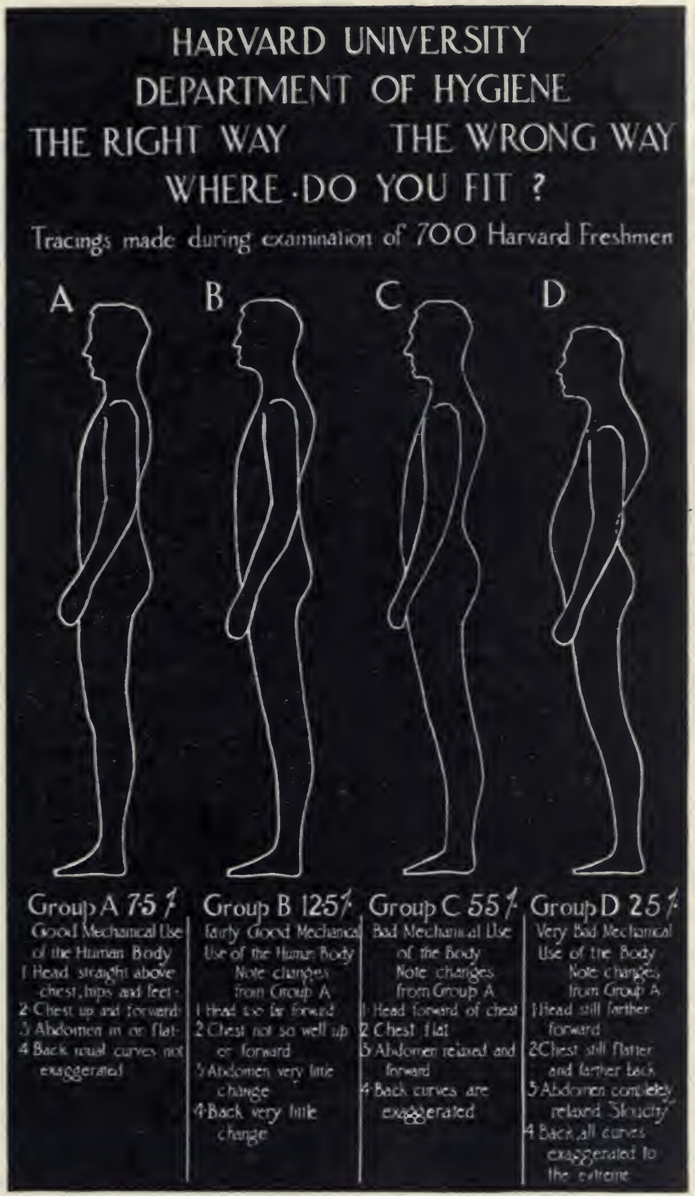
The difference in the human body is not confined to its outward shape alone. The roentgen-ray shows extremes of differences in the frame-work and also in the position and shape of the internal organs. There will also be every degree of variation between the extremes. The normal, therefore, cannot be found by taking the average of a large number of measurements of the ordinary individual since these measurements would be open to the same criticism that would apply to a series of measurements and weights of spleens of individuals who lived in a malarial country. The measurements so taken would only be the average for the people of that particular section of the country and not necessarily for the rest of the world. The standard of normality, therefore, cannot be based on averages but must be based on what is considered the *ideal* for a given type of individual. The human machine may be far from this standard and yet be very efficient. Many of our most successful men of the day are incapacitated physically but they have gained their success *in spite* of their disability.

In order to form an opinion of what constitutes mechanical perfection, it is necessary first of all to have a mental picture of the body. This picture is made up from a combined knowledge of the anatomy of the body and the mechanical changes which may come in the various positions which the body assumes; from what may happen to the internal shape of the thoracic and abdominal cavities in these various positions, and to the organs in these cavities as the cavities change their shape. It is impossible in an article of this length to give a picture of the mechanics of the body as a whole, but fortunately this is not necessary since the mechanical principles which govern a particular part or organ may be applied to the whole body. Take for example the spine. When the bones, muscles and ligaments of the spine are in a position which allow equal motion in any direction then they are being used in a position of least strain and are mechanically most efficient. When, on the other hand, they are used at one limit of their motion, they are mechanically inefficient because one group of muscles and ligaments has to do more than its normal work, and the result is strain.

This mechanical principle of using the spine at a point not at either extreme of its curves or range of motion but at some midway point can be applied to all other parts of the body. Take, for example, the chest. In the perfectly aligned human machine, the lower ribs at the axillary line in the ordinary standing position will have wide intercostal spaces. In the human machine with the bad bodily mechanics the ribs will be found to be very close together, or even over-riding. This crowded position, which can only mean strain, is a physical defect and is necessarily associated with other malalignments, such as a flat chest, a rounded dorsal spine, a forward head and a protuberant lower abdomen.

It is, of course, only possible to form an accurate opinion of the mechanics of the body by a complete examination of the body with the clothes off.

The question naturally arises, does poor posture or bad bodily mechanics have any effect on the health of the individual? In order to get some data by which to form an opinion of this kind, a careful examination was made of all men in the freshman class at Harvard University, attention being paid not only to the usual medical examination but also to the posture or the bodily mechanics of each man. A tracing was taken of each one, and when these tracings were collected and studied they were found to fall naturally into four groups which for convenience were designated, A, B, C, and D (Fig. 1). Of the 700 men examined, 7.5 per cent. were in Group A, 12.5 per cent. in Group B, 55 per cent. in Group C, and 25 per cent. in Group



HARVARD UNIVERSITY
DEPARTMENT OF HYGIENE
THE RIGHT WAY THE WRONG WAY
WHERE DO YOU FIT ?
Tracings made during examination of 700 Harvard Freshmen

Group A 7·5 %
Good Mechanical Use of the Human Body
1 Head straight above chest, hips and feet.
2 Chest up and forward.
3 Abdomen in or flat.
4 Back usual curves not exaggerated

Group B 12·5 %
Fairly Good Mechanical Use of the Human Body
Note changes from Group A
1 Head too far forward
2 Chest not so well up or forward
3 Abdomen very little change
4 Back very little change

Group C 55 %
Bad Mechanical Use of the Body
Note changes from Group A
1 Head forward of chest
2 Chest flat
3 Abdomen relaxed and forward
4 Back curves are exaggerated

Group D 25 %
Very Bad Mechanical Use of the Body
Note changes from Group A
1 Head still farther forward
2 Chest still flatter and farther back
3 Abdomen completely relaxed "Slouchy"
4 Back, all curves exaggerated to the extreme

Figure 1.

D. In other words, 20 per cent. of the men used their bodies in good or fairly good mechanical lines, and 80 per cent. in bad mechanical lines. The results of this classification were then compared to the medical findings which showed that no man in Groups A or B complained of backache, while over 6 per cent. in Group C and over

8 per cent. in Group D gave a history of backache. Functional albuminuria was much more common in Groups C and D, and more common in D than in C. Operations for appendicitis were progressively more common as one went from A to D. These findings strongly suggest that poor mechanical use of the body may be considered a definite factor in the health of the individual.

Poor bodily mechanics are more easily prevented and corrected in childhood than in adult life, and the time spent in training at this age brings far more reaching results than the same time spent on adults. The remainder of this paper will be devoted to the report of cases among children, illustrating some of the conditions which result from poor bodily mechanics, and the improvement which may be expected when the poor posture is corrected.

CHARACTERISTIC SYMPTOMS OF EACH GROUP

Constipation.—The symptom which characterizes the first group is *chronic constipation.* Such cases are not rare even in childhood and often the patient gives a history of consulting one physician after another without relief. In many instances large doses of laxatives are required daily, and occasionally the constipation is so severe that enemas are given daily to obtain a stool. Physical examination reveals nothing abnormal except a large abdomen and lordosis which are a part of the poor bodily mechanics.

REPORT OF CASES

Case 1.—M. D., age 6½ years. When first seen in December, 1913, she had had digestive trouble, associated with constipatien, and a very large abdomen during the first and second years of her life. She came in at this time because of a painful hip which came on suddenly when getting out of bed one morning. The physical examination (Fig. 2) showed that she was of the extreme bad mechanical type with very large abdomen and the extreme flat chest. The hip showed only slight limitation of motion at the extremes, and did not exactly simulate a hip disease. The child was fitted to a brace to support the abdomen and the back, and was given simple exercises for the body. The hip trouble entirely cleared up and the constipation which had always been very troublesome gave practically no more trouble for two years. In 1917, she was again seen because she was badly constipated, had dark circles under her eyes, and tired very easily. She had not taken any exercise or worn her brace for many months. A new brace was applied and she was started on her exercises and rest periods again. When seen in June, 1919, she had had a very good winter; the digestion had been very good, and she was taking no medicine for her bowels.

Comment.—The interesting points in this case are the digestive disturbances, the constipation and the arthritis of the hip, all of which cleared up with the correction of the extreme faulty mechanics of the body.

The exercises referred to above and which with simple modifications were given in all the cases in this series, were planned not primarily to strengthen the muscles, which are always weak in these cases, and so get the child into better muscular tone and better posture, but to teach the correct posture of the body and then do a few exercises, provided the body was kept in good mechanical lines while doing the exercises. It was considered much more important to keep the body properly lined up than that she should be able to do an exercise or a series of exercises any great number of times or with any special rhythm.

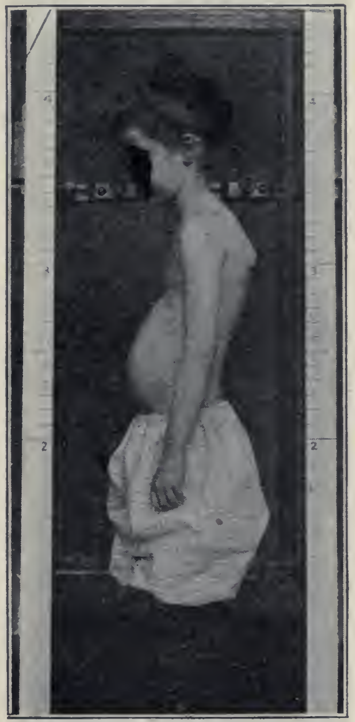


Fig. 2.—Note the extreme faulty posture, especially the flat chest and the abdomen that is more protuberant below the umbilicus than above.

The type of brace varies with the individual. In some cases a small abdominal pad which is attached to a small back pad is used, while in others the abdominal pad is attached to a spring back brace which has shoulder straps. The type of support used depends on the condition of the child and whether or not she is able to hold herself in the correct position.

The best periods referred to are carried out most carefully because it is considered that fatigue is at the bottom of a large amount of the bad postural conditions. The child is always made to lie down on its back with no pillow under the head. A small pillow is placed under the back so that it reaches from just above the hips to the middle of the scapulae. It is desirable to have the child take this position after each meal for at least one half an hour. After the noon meal a full hour is better than the shorter time.

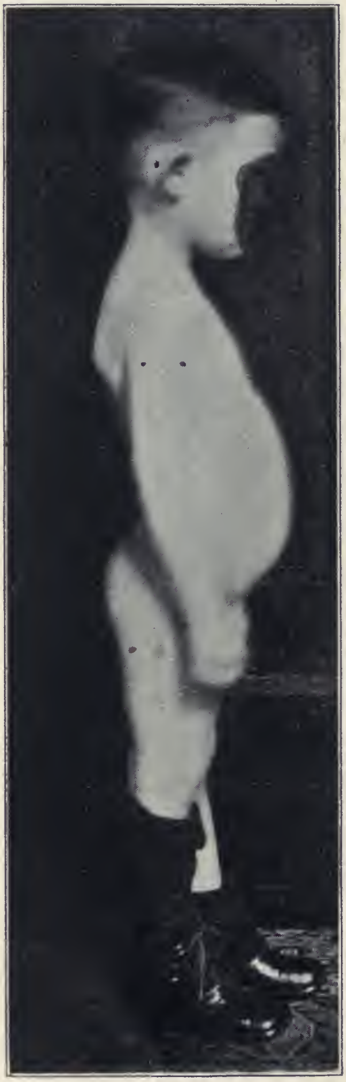


Fig. 3.—Type seen in cyclic vomiting. Note the relaxed posture, especially the prominence of the abdomen below the umbilicus.

Cases 2 and 3.—Patients, aged 5 and 3 years, respectively. These two cases are reported together because the patients were brothers and both had severe attacks of indigestion. The elder suffered from cyclic vomiting, and the younger from extreme constipation, occasional attacks of so-called "acidosis," and from a very bad temper. The attitude (Fig. 3) of the younger brother is characteristic of both children. An abdominal support was applied in each case. Reports received two years later from the father, who is a physician, state that both children were much better, that the vomiting had stopped and the constipation had become negligible. Several attempts were made to leave the support off the younger boy, but each time without success. It was always necessary to go back to it because he became constipated, acted tired, and had very dark circles under his eyes. After wearing the support for two winters, both the boys went without it for the summer.

Comment.—In these cases, as may be expected in others, the abdominal support took enough strain off the lower abdominal muscles so that they tightened up and changed the shape of the abdomen, making it more prominent above the umbilicus than below, a condition that is found in the presence of good bodily mechanics. When this condition has been reached, it is possible to do without the support and get along with only the corrective exercises, provided that the child does not get overtired from one cause or another. When a child has once learned the correct use of its body it never forgets it, any more than a person forgets how to skate, but in order to keep in good condition it is very necessary that the exercises should be kept up in order to prevent a relapse into the position of bad posture.

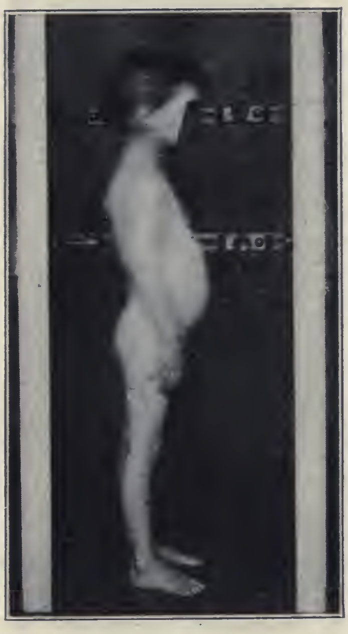


Fig. 4.—Note the extreme relaxed posture with the abdomen large, especially below the umbilicus.

Case 4.—W. L., aged 7 years, gives a history of always having been constipated and tired. Whenever he had a cold he would vomit several times at the onset, and the urine would show large amounts of acetone. His physical examination was made frequently and was always negative except that he always looked fagged out, had deep circles under his eyes, and flabby musculature. His posture was extremely poor (Fig. 4); the abdomen being prominent and relaxed especially below the umbilicus. The feet were relaxed and pronated, and there was marked lumbar lordosis. An abdominal and back support was applied and he was given corrective exercises. The constipation became less and less marked, and he grew stronger and had more vitality.

He is now in good general condition, is no longer constipated, has passed through two winters without any illnesses, and is able to meet the requirements of his life with fewer upsets. He continued to wear his support for three years.

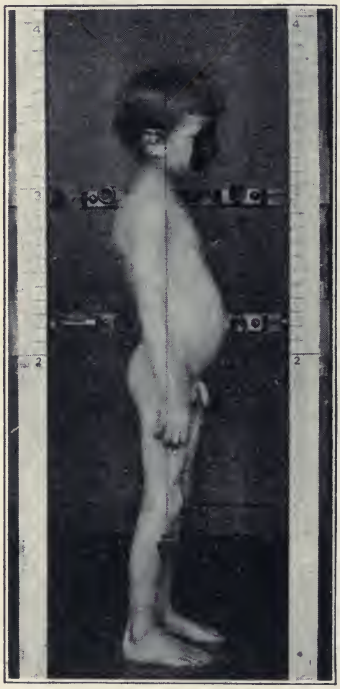


Fig. 5.—Brother of child shown in Figure 4. Note the same condition.

This length of time could have been considerably shortened if the directions for rest and corrective exercises had been more closely followed out. With the change in body posture came changes in general appearance and actions which were very striking. Although all other medical methods of treatment had been tried without any good results, improvement came very quickly after the new method of treatment was instituted.

Case 5.—A. L., aged 10 years +, gives a similar history to that of his brother (patient, Case 4). The mother described him, at 2½ years, as being "lifeless and white as chalk." He was always tired and always vomited at the onset of every infection. The physical examination at 3¾ years of age showed a very bad mechanical alignment of the body with a flat chest and a relaxed abdomen which was especially prominent below the umbilicus (Fig. 5). At the time of the first examination he was given only some simple instruction in the proper way to use his body. The following year, when seen again, the mother said that he had had an excellent summer, but since returning to the city and going to school he had been getting progressively more tired and fussy. He had lost all he had gained by his exercises because they had been given up. A spring brace was, therefore, applied and new instructions given in the proper use of his body. The last examination, at 10 years of age, showed that the boy had a large chest with firm muscles, but he still stood in a very relaxed position which he could correct very easily. He no longer looked fatigued and was better able to stand the stress of city life. As in Case 4, the correction of the extreme faulty mechanics by the brace and the relief from strain which the brace gave, prevented the overfatigue which had previously handicapped him, and made it possible for him to develop normally.

It was interesting to note the general improvement in all these cases after the application of the anteroposterior pad and back brace. When the strain was relieved the children immediately became better natured and happier, played with greater zest, and were less nervous and irritable. After supplying the supporting belt, the constipation also showed immediate improvement for about two weeks and then relapsed, after which it improved until finally it was entirely cured and normal evacuations of the bowels obtained without the use of any drugs.

These cases are examples of the type of individual who is constipated for years, tries one physician after another without success, and if left to themselves will live a "dragged out" existence, depending on laxatives for any well-being at all. Correction of the bodily mechanics may be expected to save the patients many years of poor health and give them normal bodily vigor.

Cases 6, 7, 8, 9 and 10 are illustrative of cyclic or recurrent vomiting. All of these patients were first treated by the usual dietetic methods with some improvement but without cure. Drugs and alkalies did not prevent the recurrence of the attacks, and it became clear that some other factor than diet played a part in the production of symptoms. They were finally treated from the point of view of faulty bodily mechanics and ptosis with the following results.

Case 6.—A. W., a boy, was first seen in 1916 at the age of 5 months. After weaning he was tried on modified milk and had a convulsion accompanied by a good deal of colic and gas. The physical examination at that time was normal. A wet nurse was obtained and the child did well. The following year, at the age of 16 months, he was seen because of repeated stomach upsets and constipation with constant presence of gas in the bowels. The stools then showed a tremendous amount of fat under the microscope. The symptoms improved by reducing the amount of fat in the food, but he continued to be constipated and required a laxative each day. In March, 1917, at the age of 1½ years, the physical examination showed a well nourished child with flabby flesh and somewhat pronated feet. A bismuth roentgenoscopy showed a large stomach containing an unusually large gas bubble, and a great deal of gas in the colon. The examination was unsatisfactory because of the age of the child and his inability to hold the enema. The transverse colon was seen to be of the hammock type. The point of special note was that the abdomen was very large and was most prominent below the umbilicus. An abdominal belt of cloth was applied which was to be worn temporarily night and day. A report a month later said that there had been a great deal of improvement. In May, 1920, at the age of 4½ years, he had been free from attacks for more than a year and a half, had dispensed with the belt, and was developing like any normal child.

Case 7—B. W., female, aged 5 years, 7 months, illustrates a condition in which vomiting was a much more severe symptom. She had had no illnesses until August, 1916, when she was 2 years old. She then commenced to have attacks of recurrent vomiting, the first in 1916, followed by others in June and August, 1917, and a severe attack in May, 1918. From then on she had attacks once in three months, which lasted about four days. At first the child vomited a little slimy material, after which she vomited whatever was taken by mouth. The bowels were usually cleared out with calomel and at first hard stools were started. Even though she took no food for three or four days, she had a large sized stool by enema each day. Between attacks the child was a very hearty eater and was troubled with constipation. A roentgen-ray report showed that the stomach was normal in outline but rather large. There was definite delay in emptying, but there was no marked abnormality in position of stomach or colon. The roentgenogram did not show any marked ptosis and ruled out obstruction in the region of the appendix, which was freely movable.

The physical examination showed an extremely relaxed posture with the shoulders drooped and the head forward. The chest was very flat and narrow anteroposteriorly. The lower ribs were somewhat flared outward. The abdomen was large and flabby and protuberant below the umbilicus. When the child lay on her back the lower ribs flared out and became very prominent, showing a partially fixed deformity due to faulty posture. Feb. 28, 1920, the family reported that after the application of the belt, March, 1919, she made a steady improvement. The abdominal support has had to be changed once or twice, but the improvement has been constant. She has had two or three attacks since last seen, but they have been less severe, the last one lasting one day instead of four. She has gained in weight and looks much better.

May 27, 1920, the mother reported that the belt was taken off after nine months and since then has not been worn. She has had no attacks since November, 1919.

Comment.—This case presents a finding which is common to many other cases in that the stools contained excessive amounts of fat. Careful dieting and reduction of the fat resulted in some improvement but not in an entire cure of the symptoms. Application of the belt for nine months, plus the corrective exercises, apparently resulted in a complete cure, and there has been no attack in the last six months.

Case 8.—E. M., a girl, first seen in December, 1917, at the age of 5 years, with a history of having vomited for four days. The vomiting was so severe that a surgeon was called in and confirmed the opinion that the appendix was not involved. Her urine at that time contained much acetone. She did not fully recover from this, and had one severe attack and two less severe ones between then and Jan. 12, 1918. In the second of these attacks she screamed with pain in the abdomen and vomited for twenty-four hours She had been constipated for some time even though her diet had been regulated. The stools were large and sometimes light colored. The attacks were repeated frequently without any special cause, but were more apt to come on when the child was tired or excited. The physical examination showed a thin type of child standing in an entirely relaxed position without the extreme deformities one might expect (Fig. 6). The points of special note were that the abdomen was most prominent below the umbilicus and that the lower ribs at the sides were very close together and flattened in front. An anteroposterior pad was applied, the correction of the faulty posture explained, and exercises and rest periods advised. Two years later, in the spring of 1920, her parents reported that she had been free from vomiting and pain since the belt was fitted.

Comment.—This case illustrates the difficulty in determining whether in the presence of abdominal pain, a surgical condition is back of the trouble or not, and should be contrasted with Case 11. In an earlier part of the paper the increased incidence of abdominal operations in students with faulty posture was mentioned and brings up the question as to whether bad bodily mechanics does not predispose to infection of the appendix, or cause symptoms simulating those of appendicitis which result in the unnecessary removal of the appendix. The entire cessation of attacks after the application of the belt was very striking, especially as it came out at an age when a spontaneous cure could not have been expected.

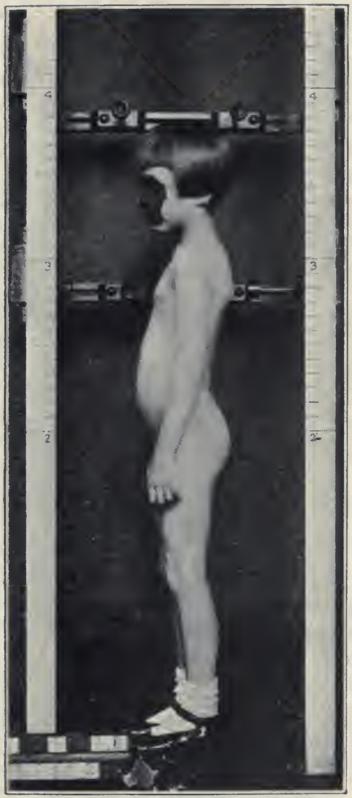


Fig. 6.—Thin type of child standing in entirely relaxed posture without extreme deformities one might expect. Note the relaxation of the lateral walls of the abdomen below umbilicus.

Case 9.—G. M., aged 5½ years, brother of patient, Case 8, had stomach upsets similar to his sister. (His mother says that she herself used to have "bilious attacks" as a child, but has outgrown them.)

He was always well up to the age of 2 years, when he commenced to have attacks of vomiting in which he would vomit for three days at a time, being even unable to retain water. These attacks would return about once in six weeks. During the attacks the eyelids often swelled up following the administration of large amounts of sodium bicarbonate given because of acetone in the urine. His stools contained a slight excess of fat between attacks. The diet was carefully regulated, and only small amounts of fat were allowed. He frequently had gas and hiccoughs and a slight cold or fatigue would bring on an attack.

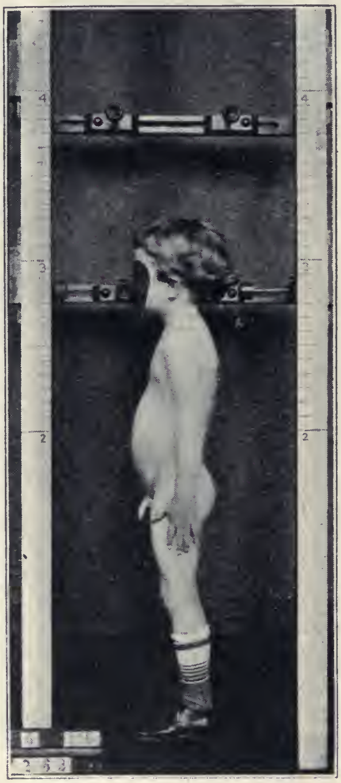


Fig. 7.—Brother of patient shown in Figure 6, taken after wearing the belt for eight months (see text). Note that the abdomen below umbilicus is not as prominent as above.

The physical examination March 28, 1917, when he was 2½ years old, was difficult to make because the child would not allow his mother to take off his clothes. It showed, however, a large red cheeked boy with markedly relaxed feet and an unusually large abdomen which could be felt through the clothes, the part below the umbilicus being the most prominent. Eight months later the examination was made without difficulty and the accompanying photograph (Fig. 7) was taken. This shows the typical posture and also that since wearing the belt the lower abdomen had become much smaller and the upper part relatively larger, a condition that one would expect to obtain with wearing a belt. After applying the belt, April 12, 1917, he had no more attacks, and has now been free from vomiting for over two years.

Comment.—This case illustrates the fact that there is a tendency for poor body mechanics to run in families. Like his sister, cure followed the application of the belt.

Case 10.—J. G. suffered from recurrent vomiting and recurrent diarrhea with marked malnutrition. She was first seen in 1914 at the age of 6 years, with a history of repeated attacks of vomiting of all food, sometimes accompanied by rise of temperature and acetone in the urine. Occasionally, the attacks would end in a mild colitis in which the stools contained mucus and at times blood. Recovery from the attacks was slow. The attacks came on at intervals of from three weeks to four months without any known cause. The physical examination was normal, aside from the fact that she was poorly developed and badly nourished with a shallow chest and a protuberant and relaxed abdomen (Fig. 8).

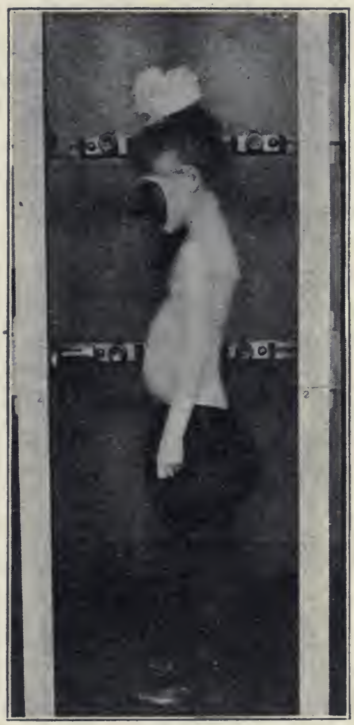


Fig. 8.—Thin type of child markedly relaxed with lower ribs flared outward. The abdomen very large below the umbilicus.

A roentgenogrm in 1914 showed that there was a large dilated atonic stomach, a greatly distended large intestine with ptosis, but no evidence of adhesions.

In January, 1914, at the age of 6 years, she was fitted to a belt and given the usual rest periods. She was on an entirely fat-free diet. After the belt was applied, she improved somewhat, but continued to have attacks every two or three weeks of vomiting and diarrhea lasting several hours and always accompanied by the presence of acetone in the urine. After a while, the intervals between attacks became longer and the vomiting less frequent and severe, but she still had slight upsets during which her breath and bowels would not be just right. Between the attacks she was very constipated. During the next year, 1915, she did not gain much in weight, but her appetite became better. After 1916 she had no more attacks of any kind and gradually commenced to do the things normal for her age.

March 11, 1920, a letter was received from the mother stating that she had done finely during the past year and had grown tall and quite stout.

Comment.—This case is interesting because after the anteroposterior pads were first applied and the proper resting positions and exercises were given, she improved and was not seen again for four years. The recurrent vomiting and diarrhea had been controlled entirely, presumably because she had persisted in the exercises and followed all directions to the letter thereby preventing overfatigue and giving her body an opportunity to compensate for the defects due to the bad bodily mechanics.

These five cases are examples of different types of cyclic vomiting all having the same physical background, faulty bodily mechanics. When these children are undressed, the relaxed abdomen, particularly prominent below the umbilicus, immediately strikes the eye. A careful study of cases of cyclic vomiting, many of them in retrospect, makes it seem probable that these children have what might be termed fractional constipation due to a lax intestinal and abdominal wall. This condition is undoubtedly accentuated by fatigue. Even though they have a movement of the bowels each day some fecal material is left behind, which gradually accumulates to a degree which causes vomiting. In two cases seen before the present method of treatment was instituted, the vomiting persisted until the children had a tremendous evacuation of the bowels, after which they sat up in bed and said they were well. Subsequent treatment and results showed that they were right.

CASE 11.—This case illustrates a condition which is not uncommon and which may be confused with cyclic vomiting, but which needs surgical interference.

D. C., a girl, aged 4½ years, had her first attack of vomiting when she was 4 years old. Following this she had two other attacks which made it seem probable that she was commencing to have recurrent vomiting. The physical examination was normal. After three days of vomiting her abdomen was sunken and easily palpable everywhere, and there was no dullness, tumor or tenderness. On standing, the abdomen seemed to be relaxed. A belt was, therefore, put on and she was given exercises. The fat in her food was reduced because her stools showed a slight amount of fat, but despite the abdominal support, the attacks of vomiting continued.

Subsequently, roentgenoscopy showed dilatation of the small intestine just above the ileocecal valve and the large intestine practically empty. This was interpreted as evidence of obstruction at the ileocecal valve due to a diseased appendix. The operation showed a chronic appendix with adhesions

Comment.—This case brings out two points, first, that in all cases of recurrent vomiting the possibility of a chronic appendicitis must be ruled out, and, secondly, when there is inflammation of the appendix, abdominal support cannot be expected to affect it favorably.

The third group of cases illustrates the symptom complex of chronic constipation associated with attacks of severe abdominal pain. In some of the cases, there was vomiting which was so alarming that in two of them abdominal operations were considered, and in the third case an operation was performed for acute intestinal obstruction. The histories of these cases are similar to those of the preceding group, except that in the one vomiting was the prominent symptom and in the other the abdominal pain.

Case 12.—E. S., a girl, was first seen at the age of 13 months. She was a normal child at birth and was breast-fed for five months. After that she had a difficult feeding history in which the prominent symptom was constipation with large amounts of gas in the bowels. At one year, she commenced to have attacks of violent pain in the abdomen. The stools showed a large excess of fat under the microscope and she was, therefore, put on a diet with part of the cream removed from the milk, but still continued to have considerable gas in the bowels which caused her to wake up from a sound sleep crying. She was also habitually constipated. The mother came to the conclusion that if the bowels were not moved they would finally block up and cause an attack of pain with fever and vomiting, the attacks coming at intervals of from two to three months. During the attacks the stools were usually undigested and contained an excess of fat with much mucus in spite of the fact that some of the cream was removed from the milk. During the second year she had four or five such attacks, at the end of which time a cloth belt was applied because of her protuberant lower abdomen. After this she became somewhat less constipated, but still required a laxative. She continued to improve in general condition, looked better, and went through several respiratory infections without vomiting or attacks of pain. Oct. 29, 1917, a spring back brace was applied because of the continued constipation, after which she was much better. From then on up to date, that is, in the last three years, she has had no more attacks of pain or digestive upsets, although she has been through several illnesses.

Comment.—This case is interesting because it is an example of a child who developed symptoms at a very early age, 13 months, before the upright standing position could be expected to play a part in the body mechanics. It illustrates further that it is practical to apply a belt at a very early age.

Case 13.—L. B., a girl, commenced to be constipated at 4 months of age. She was found to be unable to digest cream. At 5 years of age she complained of headache off and on. At 5½ years she had an attack of indigestion with a temperature of from 99 to 100 F., and she was nauseated and cried because of severe abdominal pain. Enemas brought away considerable gas, but no feces; they gave temporary relief from the pain. Her physical examination was normal, except for gas and tenderness in the lower bowel. The continued abdominal pain suggested an acute appendicitis, but the surgeon who saw her in consultation did not think that the appendix was the source of the trouble. In the next few days the stools contained large amounts of mucus with a small amount of fecal material. The pain then gradually disappeared. During the next six months she had two more attacks of pain, looked pale and run down, and was found to have pus cells in the urine. The pyelitis resolved itself, but the constipation continued, and in the fall of 1914 she had another attack of severe abdominal pain with gas, which was relieved by an enema. At this time it was noted that she had a shallow chest and a large relaxed abdomen (Fig. 9).

In December, 1915, a spring back brace was applied. She wore it for six months, at the end of which time the brace was dispensed with and an anteroposterior pad was applied. The constipation gradually disappeared during this time and she had no more attacks of pain. She has now been well and without treatment for over four years.

Case 14.—E. S., a boy, when 2 years old commenced to cry out in the middle of the night for no apparent cause, following which he would have attacks of high temperature. At that time he had what was said to be a fat indigestion and the fat in the food was reduced with immediate improvement. In 1912, when he was 3 years old, he had grip with otitis media followed by enlarged glands in the neck, which eventually broke down and were thought to be tubercular. This, however, was not proven. In 1914 he was very constipated and was given Russian mineral oil, which resulted in satisfactory movements of the bowels, and he became better and gained weight.

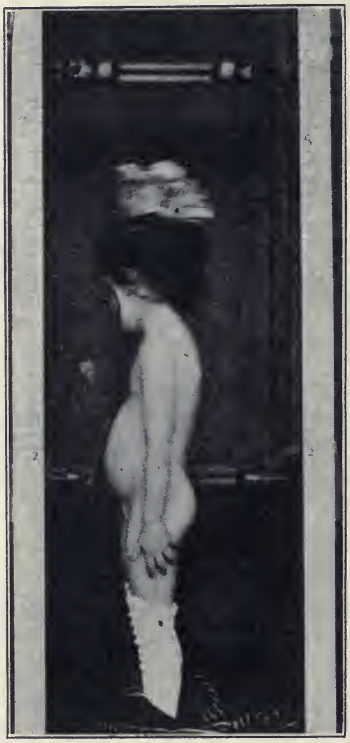


Fig. 9.—Note the extreme faulty posture with the very large abdomen which is most prominent below the umbilicus. Note also the forward position of the head, flat chest, and the increased curves of the back.

Jan. 20, 1917, he had a sudden attack of severe abdominal pain and nausea. The pain was in the left upper quadrant of the abdomen and was relieved temporarily by a laxative and the passage of much gas. From then until January 23, he continued to have pain. On the twenty-third he suddenly sat up after a movement of the bowels and said he was well. In February, 1917, he had another similar attack of pain lasting two days, with a temperature of 99 F. March 5 and 6 he had a third attack of pain with a temperature of

102 F. Enemas were given on all of these occasions and brought away much fecal material and gas, after which the symptoms were relieved. March 8 and 9 he had a mild attack. Roentgenograms showed that he had a redundant colon with a loop in the splenic flexure, which came down two-thirds of the way to the sigmoid.

A physical examination showed a very delicate boy with bright red cheeks. His posture was that of complete relaxation with a very large bloated abdomen. In spite of the size of the upper abdomen, the lower abdomen was even more prominent. The abdominal musculature was negligible because it had been stretched out as a result of the distention. The lower ribs were very much flattened and flared outward. An anteroposterior pad was applied for day wear and a webbing belt for night wear. There was also ordered a very careful routine of rest to be taken in special positions to correct the faulty mechanics as well as to keep him quiet. The importance of the rest in these cases cannot be overemphasized.

The attacks of pain were relieved somewhat, and finally became less frequent and severe, and he commenced to gain in weight and have very large movements of the bowels. During the summer of 1918 he had pain off and on in the left upper quadrant. A new brace was fitted in October, and the attacks of pain finally stopped entirely in January, 1919. From then on his convalescence has been uneventful and for the past year and a half he has been considered a normal boy.

Comment.—This case is an example of recurrent attacks of pain in the splenic region with vomiting and symptoms simulating obstruction. The symptoms were so severe that two internists and a surgeon thought that an exploratory operation should be performed. It was not until the mechanical element was taken into account and an abdominal support was given that relief was obtained. This case also illustrates the point that the wearing of a support by patients who have a large distended abdomen, even though the child is in bed, will relieve a serious and painful condition.

Case 15.—H. C., a boy, was first seen in July, 1916, at the age of 11 years, with the following history:

At 3 years he had an acute attack of diarrhea which was probably an infectious diarrhea. At 5 years he commenced to have attacks of abdominal pain with symptoms of intestinal obstruction which were thought to be due to a recurrent appendicitis. He was operated on at this time and found to have a definitely chronically inflamed appendix with adhesions of the ileum. After this he was perfectly well for a time, but the attacks returned again at the end of six months. The attacks always followed overeating, mental or physical fatigue, and were accompanied by pain and sometimes nausea. The pain during the attacks was so severe that it caused him to cry out and his face to break out in perspiration, but it was not necessary to use opiates. The boy found that the pain was relieved somewhat if he tied a towel tightly around his lower abdomen during these attacks. When the bowels were thoroughly cleaned out the abdominal symptoms would disappear.

The intervals between attacks then lengthened out and he was having only one attack every six months, until the year previous to his visit to me when the attacks again increased in number and in the last three months, that is, since April, 1916, he had been having one attack after another. The last of these attacks simulated acute intestinal obstruction and he was, therefore, operated on again. Previous to this attack he had been on a very strict diet of which no criticism could be found. At this operation there were found to be adhesions in the neighborhood of the appendix. The lower part of the small intestine was found to be normal in every way, but as it was followed up there was dilatation as large as the wrist. This condition included about half of the small intestine. The mesentery over a large part of the small intestine was full of small glands, none of which, to the eye, showed any evidence of tuberculosis. There were a few glands in the region of the cecum which increased in number up to the region of the ligament of Trietz, where there were sheets of glands, the largest being the size of a bean. None of the glands were excised and nothing was found which led the surgeon to believe that there was any mechanical cause for the upset.

When seen one month later, July, 1916, his physical examination did not show anything remarkable aside from the operation scars and the fact that the lower abdomen was protuberant and apparently relaxed. The stools at this time contained a large excess of fat. The diet was, therefore, regulated accordingly.

In the fall of 1916 an abdominal pad was applied to the lower abdomen. He made a slow gain in weight and instead of being constipated and using considerable Russian mineral oil daily his bowels moved regularly with the use of an occasional cathartic, his flesh became firmer, and he was having no attacks of pain.

In February, 1917, he had an attack of grip and slight pain in the abdomen. He was then well until February, 1918, when he had an attack of diarrhea and considerable pain in the abdomen, which was relieved by passing gas and bloody stools.

In June, 1918, he was doing very well and having very little pain. In March, 1919, he reported that he had had an exceptionally good winter, with only two slight upsets, both of which followed eating food at boarding school which caused the other boys also to have digestive upsets. During most of this time he had been wearing the abdominal support. He found that when there were any signs of discomfort the belt relieved the symptoms very quickly.

During the past year he dispensed with the abdominal support and has been free from the attacks of pain.

He is now 16 years old (1920), takes slight part in athletic sports, rides horseback, and with a little more careful diet than most boys of his age, lives a normal life.

Comment.—This case illustrates a situation in which everything that was possible surgically was done for the boy, but despite this the attacks of pain recurred with equal severity until the abdominal support was applied, and both the parents and the boy are convinced that the belt is responsible for his well being. He says he is able to prevent the recurrence of symptoms by putting on the belt at the earliest premonitory sign.

SUMMARY

1. Faulty bodily mechanics was responsible for a great loss of efficiency among adults in the war.

2. Correcting it, changed many inefficient men into efficient soldiers.

3. It is common to all ages and is surprisingly prevalent.

4. It is easily corrected and can be done so most economically during childhood.

5. It is responsible in most instances for diminished powers of digesting fat in children.

6. It is the cause of a certain amount of chronic constipation.

7. It is the background and probably the cause of many if not most cases of recurrent vomiting.

8. In many instances the symptom of acute abdominal pain in children, when associated with chronic constipation, is due to poor bodily mechanics. These symptoms are often so severe that they are confused with those of acute intestinal obstruction due to other causes.

9. In the cases cited in which the faulty body mechanics have been corrected, in connection with the other treatment, the patients have all shown a more speedy recovery than is seen in cases without this correction. This makes us feel that the element of body mechanics is one which should always be considered in these types of cases.

THE CIRCULATORY REACTIONS TO GRADUATED EXERCISE IN NORMAL CHILDREN *

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INTRODUCTION

Recent experience at the army camps has demonstrated the importance of physical training in the adult. We know that exercise is necessary for normal children, since it is indispensable for proper development of the skeletal muscles, the heart and lungs; and latterly the medical profession has come to appreciate that exercise is also important for children with chronic valvular disease. It is very difficult to decide on the amount of exercise to be allowed a patient with cardiac disease. The subjective symptoms and objective findings following given exercise have been depended on to determine the "exercise tolerance." Individual interpretation of clinical symptoms in children is naturally limited and variable, and here it also must be remembered that there is a certain element of error in a child's estimate of its subjective sensations following exercise. For these reasons, any additional facts in estimating the "exercise tolerance" would be of great value.

Bainbridge[1] states that the range of a man's ability to take exercise is usually determined by the functional capacity of his heart. Although exercise taxes the resources of the circulatory and respiratory systems equally with those of the muscles, the heart, as a rule, reaches the limit of its powers earlier than the skeletal muscles, and its functional capacity determines a man's capability for exertion.

According to Mackenzie,[2] the functional efficiency of the heart muscle depends on the reserve force, and exhaustion of this reserve force may be physiologic or pathologic, both more or less alike, except that the latter occurs with greater facility. Most of the tests of the function of the heart in adults are based on the circulatory

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* Read before the Section on Diseases of Children of the American Medical Association at the Seventy-First Annual Session, held April 26-30, 1920, at New Orleans.

[1] Bainbridge, F. A.: The Physiology of Muscular Exercise, Longmans, Green & Co., pp. 3 and 187.

[2] Mackenzie, Sir. J.: Principles of Diagnosis and Treatment in Heart Affections, Henry Froude, Oxford University Press, 1916, p. 40.

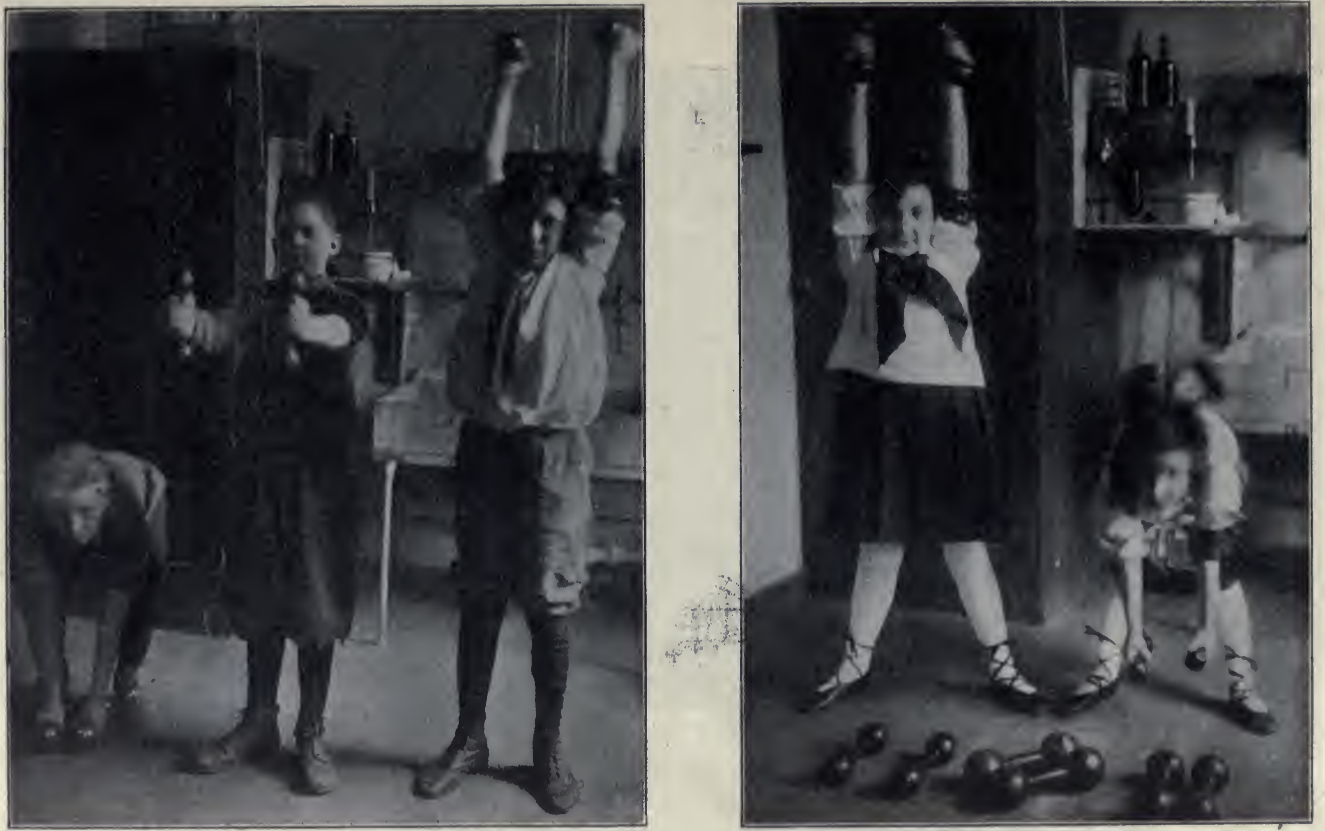

Figure 1

Figure 2

Figs. 1 and 2.—Movements during test exercise. The dumbbells are swung from the floor to the full stretch of the arms overhead, describing an arc, and back again between the legs. There is no pause between the up and down motion, or between the swings.

changes produced by muscular exertion. Such changes of pulse rate and blood pressure have been considered to be important criteria of the heart's function.

Reports in the literature of the circulatory reactions after exercise in children are limited to change of pulse rate, since heretofore estimation of blood pressure in children has not been considered to be of clinical value, and a review of the literature does not show any work on the circulatory reactions after exercise in children, similar to that of Barringer [3] and Cotton, Rapport and Lewis.[4]

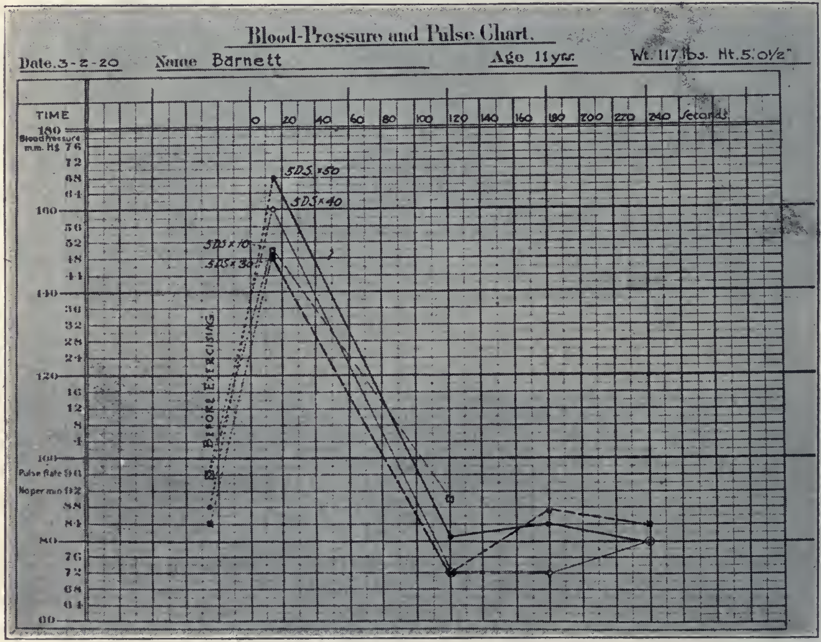

Fig. 3.—Chart of typical curves of pulse immediately following series of increasing amounts of exercise, at a constant rate of two seconds per swing. Two 5-pound dumbbells swung ten, thirty, forty and fifty times. Zero line represents end of exercise.

The present study was, therefore, undertaken to ascertain whether the circulatory reactions after exercise in normal children were similar to those found in adults, and whether in these reactions anything can be found to act as a guide or check in estimating the "exercise tolerance."

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[3] Barringer, Theodore B., Jr.: Studies of the Heart's Functional Capacity, Arch. Int. Med. **20**:829 (Dec.) 1917.

[4] Cotton, T. F., Rapport, D. L., and Lewis, T.: After Effects of Exercise on Pulse Rate and Systolic Blood Pressure in Cases of "Irritable Heart," Heart, **6**:269, 1917.

TECHNIC

Similar experiments on circulatory reactions after exercise in normal adults, reported by Barringer and Cotton, Rapport and Lewis were closely followed. My investigations were conducted on twenty average normal children between the ages of 6 and 13, sixteen boys and four girls. Repeated observation of pulse rate, systolic blood pressure and clinical symptoms following the termination of graded test exercises were noted on each child. The period of observation was from two to eight weeks, at two day intervals. In all, more than five hundred individual test exercises were given, comprising one hundred and fifty complete experiments; each experiment consisted of three or four graded test exercises.

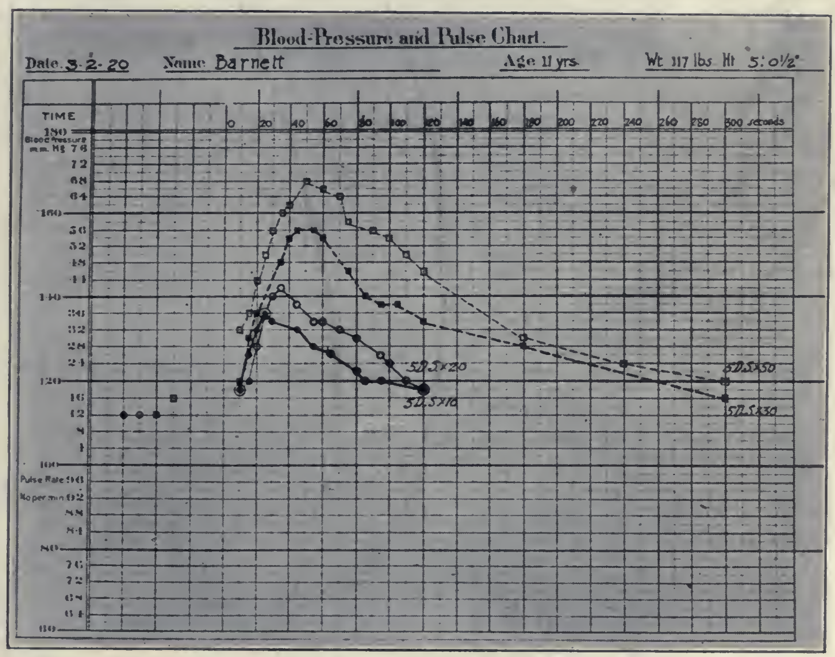
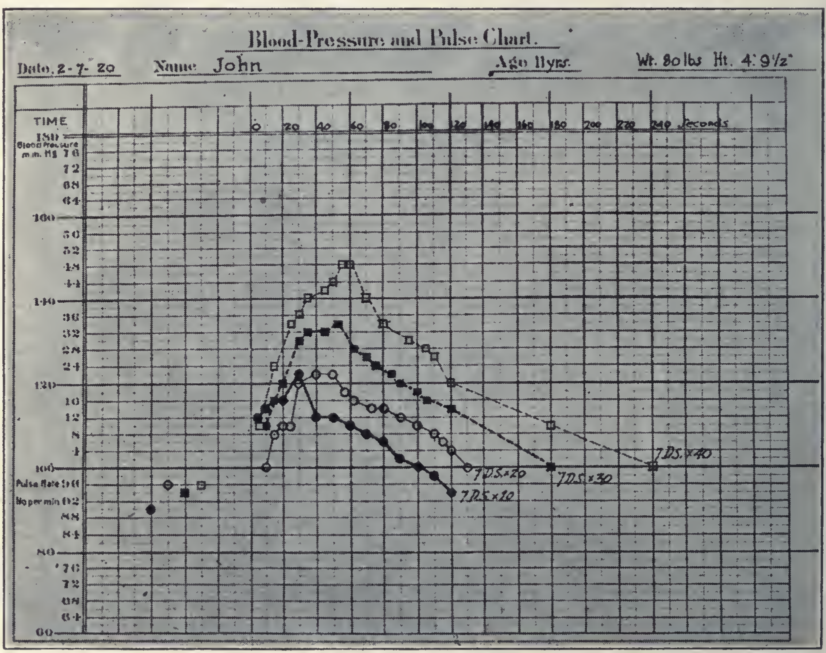


Fig. 4.—Chart of typical curves of systolic blood pressure reactions immediately following exercise as described in Figure 3. Controls noted to left of zero line; work to right of curves.

The test exercises consisted of swinging one or two iron dumbells (3, 4, 5, 7 and 10 pounds each) from the floor to the full stretch of the arms overhead, and back again between the legs, *at a constant rate of two seconds for each swing* (Figs. 1 and 2). This movement was repeated from ten to sixty times to increase the amount of work. Each child performed at one visit three or four of these exercises, graded from moderate to severe, until the *maximum* effort was approached, as evidenced by marked breathlessness, flushed face, perspiration and fatigue. This was corroborated by an additional exercise of slightly increased intensity. The possible influence of one exercise on another was eliminated by allowing a full rest between each exercise, and by varying the order of the exercises on subsequent visits. The pulse rate at the wrist was taken by an assistant before each exercise until it remained constant. It was then taken immediately after exercise for fifteen seconds, and again at the end of one hundred and ten seconds after exercise, for twenty seconds. From these counts the rates per minute immediately after exercise, and at the end of two minutes, were calculated. A pulse rate within six beats of pre-exercise rate was considered normal. If the pulse did not reach normal at the end of two minutes, it was taken at half-minute intervals for from three to five minutes.


Blood-Pressure and Pulse Chart.

Date, 2-7-20 Name John Age 11yrs. Wt. 80 lbs Ht. 4' 9½"

Fig. 5.—Chart of typical curves of systolic blood pressure reactions following series of increasing amounts of exercise, at a constant rate of two seconds per swing. Two 7-pound dumbbells swung ten, twenty, thirty and forty times.

The method used to obtain the systolic blood pressure curve following exercise was that of frequent readings at five and ten second intervals as described by Rapport. In some instances, the method of infrequent readings as described by Barringer was utilized. The instrument used was an accurate mercury sphygmomanometer, with a

9 cm. child's leather cuff, which remained on the arm during exercise. The blood pressure readings were taken by auscultation with the child in a sitting posture (Fig. 3). The systolic pressure was read before exercise until a constant level was reached and at frequent intervals for two minutes as a control, to eliminate possible variations due to cuff pressure. To obtain early readings of systolic pressure immediately after exercise, the child was instructed to sit down quickly and quietly, the plug was inserted into the cuff, and the first pressure read within ten seconds; and subsequently, at intervals of five seconds, until a maximum reading was obtained. Later, readings were taken at ten second intervals until the reading was within six millimeters of normal. No difficulty was experienced in obtaining early readings without the use of the apparatus described by Rapport.[5] The assistant noted the time exercise ceased, and the time the readings were made.

CIRCULATORY REACTIONS AFTER EXERCISE

1. *After Effect of Exercise on Pulse Rate.*—Immediately after exercise the pulse rate was markedly increased, the rise being between five and one hundred beats per minute; the maximum rate recorded was 174. In 63 per cent. of the experiments, the rise of pulse rate was apparently proportional to the increase of work performed; in 60 per cent. the maximum rate accompanied the maximum amount of work. In 57 per cent. of the experiments, the time required to reach the normal was two minutes; in 28 per cent. the pulse dropped below the normal at the end of two minutes. In 13 per cent. the pulse was above normal at the end of two minutes. It is rather surprising to note that in the majority of the experiments following maximum effort, the pulse reached normal within two minutes in spite of symptoms of marked dyspnea and fatigue, so that the "exercise tolerance" in these experiments could not be determined from the pulse rate (Fig. 3).

2. *After-Effect of Exercise on Blood Pressure.*—Normal curves of systolic pressure following immediately after moderate test exercises which are performed with ease and without subsequent dyspnea or fatigue show a steep rise a little above resting level, reaching its maximum or summit within from twenty to forty seconds, and falling quickly to pre-exercise level within two minutes (Fig. 4). Curves of systolic pressure following immediately after the severest test exercises, where the limit of effort is approached, judging from the degree of dyspnea and fatigue, show an increased rise with a prolonged period of rising, or a delayed rise or summit, reaching its maximum after from fifty to seventy seconds, and falling slowly to pre-exercise level within from three to five minutes (Fig. 5). This type of curve

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[5] Rapport, D. L.: Arch. Int. Med. **19**:981 (June) 1917.

CIRCULATORY REACTIONS AFTER EXERCISE IN TWENTY NORMAL CHILDREN

Subject	Test Exercise: Swinging Dumbbells			Systolic Blood Pressure							Pulse				Dyspnea	Flushed	Pallor	Ver- tigo	Fatigue
					After Exercise							After Exercise							
	No. of D. B.	Wt. of, Lbs.	Swings, No. Times	Before Exer- cise, Mm	First Read- ing, Mm.	Time of in Sec.	Maxi- mum Read- ing, Mm.	Time of in Sec.	Rise, Mm.	Return to Normal in Sec.	Before Exer- cise, Rate	Maxi- mum Rate	Rise	Return to Normal in Sec.					
W. (1) Boy, 7 yrs.	2	5	10	90	100	10	108	30	18	120	84	104	20	120	..	+			
Wt., 57 lb.	2	5	30	88	108	10	122	55	34	240	84	102	18	120	++	++	..	..	+
Ht., 47 in.	2	5	40	88	100	7	128	80	40	260	72	120	48	120	++++	..	++	+	+++
J. (2) Boy, 9 yrs.	2	7	10	90	100	8	110	40	20	120	84	132	48	120	..	+			
Wt., 70 lb.	2	7	30	94	100	10	116	35	22	180	84	160	76	120	+	++			
Ht., 54 in.	2	7	30	96	100	10	128	50	32	240	84	162	78	120	+++	++	..	..	+
	2	7	40	90	108	8	130	70	40	300	96	152	56	120	+++++	..	++	+	+++
J. (3) Boy, 11 yrs.	2	7	10	90	112	5	122	30	32	120	92	132	40	120	..	++			
Wt., 80 lb.	2	7	30	94	110	10	134	55	40	180	84	104	20	140	+++	+++	..	..	++
Ht., 57 in.	2	7	40	94	110	8	148	60	54	240	84	124	40	140	++++	..	+	+	+++
V. (4) Boy, 10 yrs.	2	7	10	100	118	15	118	15	18	120	80	140	60	120	..	++			
Wt., 82 lb.	2	7	20	104	110	10	134	50	30	180	82	150	68	120	+++	+++	..	..	+
Ht., 52 in.	2	7	25	104	110	5	144	55	40	240	80	156	76	120	+++++	..	++	+	++
J. (5) Boy, 12 yrs.	2	7	10	118	130	10	134	30	16	120	100	148	48	120	+	++			
Wt., 66 lb.	2	7	20	118	122	10	146	50	28	180	90	144	54	120	++++	+++			
Ht., 52 in.	2	7	30	120	140	10	160	52	40	240	100	168	68	180	++++++	.	+	+	+++
W. (6) Boy, 6 yrs.	2	3	10	88	90	10	106	30	18	120	80	112	32	120	..	++			
Wt., 55 lb.	2	3	30	94	98	10	110	50	16	180	80	132	52	120	++++	+++	..	..	++
Ht., 43 in.	2	3	40	100	102	10	124	60	24	240	88	128	40	120	+++++	..	..	+++	+++
P. (7) Boy, 11 yrs.	2	5	10	108	112	10	120	25	12	120	84	108	24	120	+	+			
Wt., 65 lb.	1	10	20	110	110	10	132	55	22	240	84	120	36	120	+++	++			
Ht., 51 in.	1	10	40	108	110	10	152	80	50	300	84	152	68	120	++++	..	++	..	++
J. (8) Boy, 10 yrs.	2	5	10	108	100	10	136	40	28	160	88	120	32	120	+	++			
Wt., 83 lb.	2	5	30	108	110	10	150	55	42	200	88	144	56	120	++++	+++	..	..	+
Ht., 51 in.	2	5	40	112	118	10	152	70	40	300	88	160	72	160	++++++	..	++	+	+++
B. (9) Boy, 11 yrs.	2	5	10	112	118	10	136	25	24	120	96	152	54	190	..	++			
Wt., 117 lb.	2	5	30	118	122	10	146	47	28	180	84	124	40	120	+++	++			
Ht., 62 in.	2	5	40	118	120	10	158	60	40	300	80	148	68	120	+++++	..	+	++	++
	1	10	40	116	120	10	156	65	40	300	84	144	60	120	+++++	..	+	++	++

B. (10)																		
Girl, 10 yrs.	2	4	10	92	94	10	102	30	10	120	96	120	24	120	..	+		
Wt., 76 lb.	2	4	30	96	100	10	114	55	18	180	96	156	60	120	++++	+++	..	..	+
Ht., 52 in.	2	4	40	96	100	10	128	60	32	240	88	160	72	120	++++++	..	..	+	+++
C. (11)																		
Girl, 6 yrs.	2	4	10	90	94	5	100	15	10	120	104	128	24	120	..	+		
Wt., 60 lb.	2	4	20	94	84	5	108	35	14	120	100	152	52	120	+	++		
Ht., 48 in.	2	4	30	94	100	10	124	50	30	240	116	160	44	120	+++	..	+	+	+
	2	4	40	98	108	5	128	55	30	240	108	180	72	120	++++	..	++	++	++
M. (12)																		
Girl, 8 yrs.	2	4	40	92	104	10	136	75	44	300	92	144	52	120	++++	..	++	++	+++
Wt., 62 lb.	2	4	30	90	106	5	134	60	44	300	92	146	52	120	++++	..	+	+	+
Ht., 50 in.	2	4	20	96	92	5	124	45	32	180	100	132	32	120	+	++		
	2	4	10	96	100	10	112	30	16	120	96	124	28	120	..	+		
R. (13)																		
Boy, 10 yrs.	2	7	10	96	96	10	102	35	6	120	84	120	36	120	..	+		
Wt., 74 lb.	2	7	30	96	98	10	114	50	18	180	84	156	72	120	+++	+++		
Ht., 53 in.	2	7	40	96	92	10	114	75	18	240	84	156	72	120	+++++	..	..	..	++
H. (14)																		
Boy, 12 yrs.	2	5	10	118	122	10	142	25	24	120	88	120	32	160	..	+		
Wt., 81 lb.	2	5	20	116	124	10	148	40	32	160	80	152	72	120	+	+++		
Ht., 58 in.	2	5	30	114	122	10	154	50	40	240	84	172	84	120	++++	+++		
	2	5	40	110	118	10	160	50	50	260	84	152	68	120	++++++	..	++	++	++
J. (15)																		
Boy, 11 yrs.	2	7	30	98	100	8	118	35	20	120	72	156	64	140	+	++		
Wt., 81 lb.	2	7	40	102	104	10	124	50	22	180	72	160	88	120	++	+++	..	..	+
Ht., 53 in.	2	7	50	104	108	10	138	55	34	300	72	140	68	120	++++	..	++	..	++
E. (16)																		
Boy, 13 yrs.	2	7	30	106	118	10	130	35	24	120	80	132	52	120	..	++		
Wt., 78 lb.	2	7	40	110	120	5	140	50	30	180	96	136	40	120	+++	+++	..	..	+
Ht., 56 in.	2	7	50	110	126	10	146	50	36	240	75	148	73	120	+++++	..	++	..	+++
H. (17)																		
Boy, 9 yrs.	2	5	20	118	118	5	142	30	24	120	88	136	48	120	..	++		
Wt., 68 lb.	2	5	30	110	110	10	138	50	28	180	100	160	60	120	+++	+++	..	..	+
Ht., 52 in.	2	5	40	110	110	10	144	60	34	240	92	160	68	120	+++++	..	++	..	++
C. (18)																		
Boy, 10 yrs.	2	5	10	136	132	10	150	35	14	120	108	140	32	120	+	++		
Wt., 84 lb.	2	5	30	120	130	10	148	45	28	180	84	132	48	120	++	+++		
Ht., 57 in.	2	5	40	122	132	10	154	50	32	240	84	160	76	120	++++	..	..	..	++
T. (19)																		
Boy, 10 yrs.	2	5	30	110	100	5	140	35	30	120	76	120	44	120	..	++		
Wt., 65 lb.	2	5	40	114	110	10	144	50	30	180	72	124	42	120	++	+++	..	..	+
Ht., 54 in.	2	5	50	110	114	10	148	60	38	240	80	114	36	120	+++++	+++	..	..	+++
J. (20)																		
Girl, 13 yrs.	2	5	20	110	106	10	138	35	28	120	84	124	40	120	..	++		
Wt., 89 lb.	2	5	30	110	108	10	146	45	36	180	84	144	60	120	++	++		
Ht., 63 in.	2	5	40	110	118	10	160	50	42	240	84	152	68	120	++++	+++	..	..	++

Tabulated average of one complete experiment on each of twenty subjects, showing reactions of pulse and blood pressure following a series of increasing amounts of exercise at a constant rate of two seconds to each swing.

is similar to that obtained by Barringer, and by Cotton, Rapport and Lewis, and is considered by Barringer to be of peculiar significance; viz., that the delayed rise of systolic pressure after work indicates that the reserve force of the heart has been overtaxed.

This type of curve showing a delayed rise and a prolonged fall was present in 88 per cent. of the experiments, and in 85 per cent. it was accompanied by clinical symptoms of marked dyspnea and fatigue.

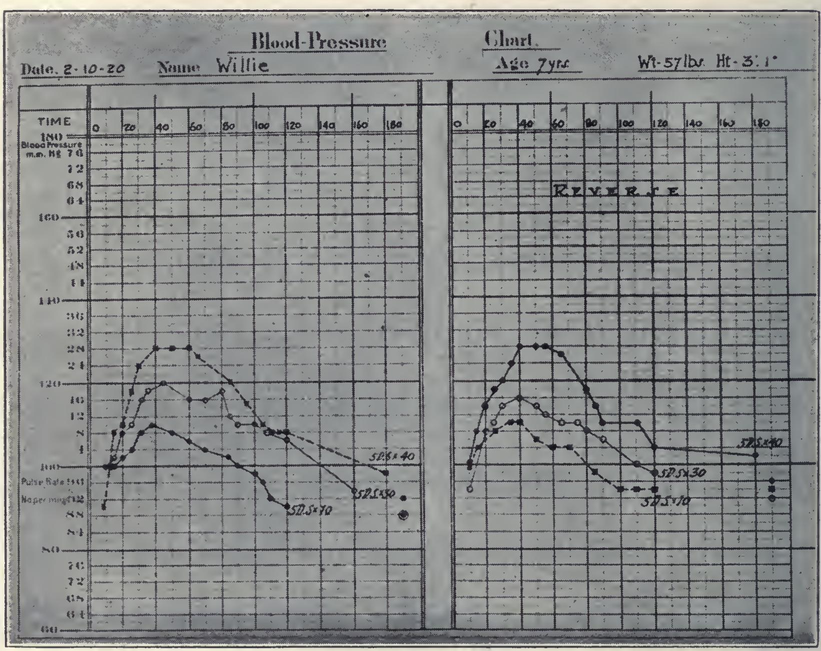

Fig. 6.—Chart showing comparative study of similar typical curves of systolic blood pressure reactions following identical test exercises on the same day, *but given in reverse order,* with one hour rest between each series.

The rise of blood pressure varied from 2 to 55 mm. The maximum blood pressure reading was 160. The rise varied directly with the increased quantity of exercise, and in 92 per cent. of the experiments the rise was proportional to the increased amount of dyspnea and fatigue.

It has been found that similar test exercises resulted in similar curves, with little variation from day to day, and a change in the order of the exercises produced no change in blood pressure curves (Fig. 6). The severest test exercise was followed by the same pressure curve (delayed rise, etc.), regardless of the order in which it was given (Fig. 7).

The effect of training was observed in that children were able, toward the close of the period of observation, to perform increasing amounts of exercise without producing this delayed rise, dyspnea and fatigue.

It was interesting to note that children who subsequently became ill, showed just before their illness and later in their convalescence, a delayed rise, dyspnea and fatigue after moderate exercise which previously had been performed without such reactions.

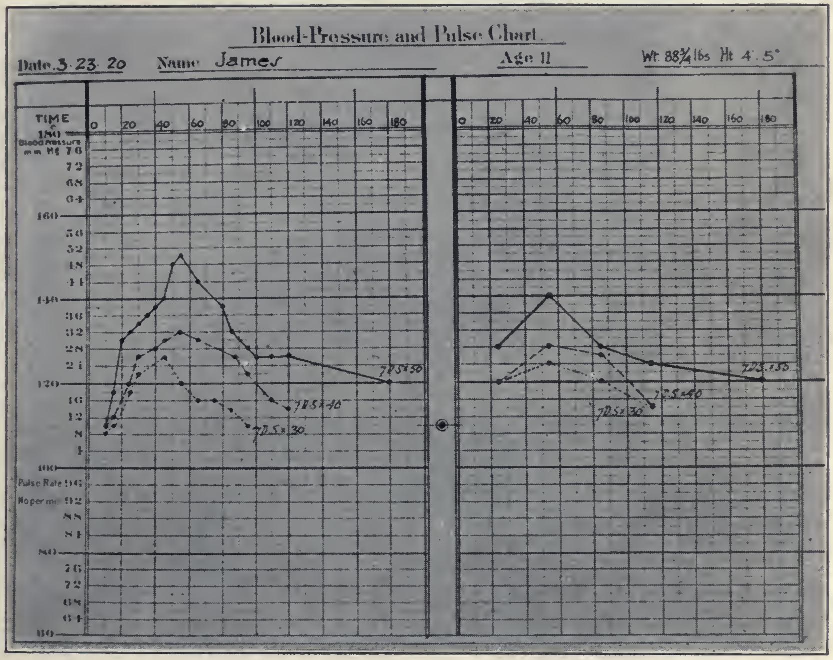

Fig. 7.—Chart showing comparative study of frequent and infrequent methods of plotting systolic blood pressure curves immediately after exercise. Curves to the left indicate frequent method of readings; those to the right, infrequent.

CONCLUSIONS

From these experiments on the circulatory reactions after exercise in twenty normal children, it may be concluded that:

1. The circulatory reactions to graduated exercise obtained in normal children are similar to those reported in adults.

2. The circulatory reactions immediately following similar graduated exercise at two day intervals over a period of weeks are, as a rule, constant.

3. The time required for the pulse rate to return to normal does not give much information as to the "exercise tolerance" of a child.

4. A type of systolic blood pressure curve after exercise, showing an increased rise, delayed rise and summit and a prolonged fall, and associated with symptoms of marked dyspnea and fatigue, would seem to indicate that the "exercise tolerance" of that particular child has been temporarily reached or exceeded.

Thanks are hereby extended to Dr. Oscar M. Schloss for his interest, and to Dr. Theodore B. Barringer, Jr., for his many helpful suggestions in this work.

I wish also to express my appreciation to Dr. Anna Kleegman-Daniels for her able assistance in conducting these experiments.

FURTHER PROGRESS IN THE STUDY OF THE RELATIVE EFFICIENCY OF THE DIFFERENT MERCURIAL PREPARATIONS

IN THE TREATMENT OF CONGENITAL SYPHILIS IN INFANTS AND CHILDREN, AS DETERMINED BY A QUANTITATIVE ANALYSIS OF THE MERCURY ELIMINATION IN THE URINE *

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ST. PAUL

The treatment of syphilis with the different mercurial preparations is still a haphazard affair, the rule being to give as much mercury as the patient will tolerate without salivation or diarrhea.

Assuming that the amount of mercury eliminated in the urine during a given time would give a fair index of the amount in the circulation, Ramsey and Ziegler made some experiments, the report of which was read before this society in 1918.[1]

From this series of experiments we were able to draw the following conclusions:

> In infants and children, mercury, when given by the month, by inunction or intramuscularly, is excreted at least partly by the urine.
>
> In new-born infants and older children mercurial ointment when placed in contact with the skin, without any friction being used (protected and sealed by wax paper from being volatilized and inhaled), is taken up by the skin and excreted in the urine and continues to be excreted in the urine for a variable time after all treatment has been discontinued.
>
> By inunction (with rubbing) mercury is readily taken up by the skin and eliminated in the urine and continues to be eliminated for a considerable time.
>
> When one inunction is given, the maximum daily amount of mercury is usually eliminated during the following twenty-four hours, smaller amounts being eliminated for a variable time.
>
> Where continuous inunctions are given, there is an accumulation in the system and considerable amounts are eliminated at intervals with only traces between.
>
> Mercury salicylate suspended in oil and given subcutaneously continues to be eliminated in the urine in appreciable amounts for eight days, or longer, the daily amounts eliminated varying widely.
>
> Mercuric chlorid by intramuscular method, a favorite method in congenital syphilis, continues to be eliminated for eight days or longer.
>
> In all cases in which mercuric chlorid was used either by mouth or the intramuscular method, protein was found in the urine.

In this new series of experiments, we have sought to determine, with some degree of accuracy, the amount and rapidity of absorption

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* From the Department of Pediatrics, University of Minnesota.

* Read before the American Pediatric Society, May-June, 1920.

[1] Am. J. Dis. Child. **16**:299 (Nov.) 1918.

of the common mercurial preparations in use as determined by quantitative estimate of the amounts eliminated in the urine.

The method is the same as that employed in the previous experiments.

It will be observed that when 50 per cent. ointment was used, the elimination began soon after administration, the maximum elimination occurring during the following three days, the elimination being fairly complete within five days.

TABLE 1.—UNGUENTUM HYDRARGYRI (50 PER CENT.) (1 GM. OF OINTMENT USED)

Name and Age	Amount and Method of Administration of Mercury	Date of Administration	Date of 24-Hour Specimen	Amount of Mercury in Mg.	Remarks
M. S., 3½ years	Unguentum hydrargyri (50%) 1 Gm. as inunction	9/24	9/25	0.50	Congenital syphilis; Wassermann positive; female
			9/26	0.60	
			9/27	0.40	
			9/28	—	
			9/30	—	
	Unguentum hydrargyri (50%) 1 Gm. as inunction	10/ 1	10/ 1*	—	
			10/ 2	0.55	
			10/ 3	0.45	
			10/ 4	0.10	
			10/ 5	+	
			10/ 6	—	
			10/ 7	—	
	Unguentum hydrargyri (50%) 1 Gm. not by inunction	10/ 8	10/ 8*	—	
			10/ 9	0.40	
			10/10	0.20	
			10/11	0.12	
			10/12	+	
			10/13	—	
			10/14	—	
			10/15	—	
L. F., 5 years	Unguentum hydrargyri (50%) 1 Gm. as inunction	4/ 5	4/ 5*	—	Normal child; female
			4/ 6	+	
			4/ 7	0.42	
			4/ 8	0.12	
			4/ 9	+	
			4/10	±	
			4/11	—	
			4/12	—	
			4/13	—	
	Unguentum hydrargyri (50%) 1 Gm. not by inunction	4/14	4/14*	—	
			4/15	+	
			4/16	0.28	
			4/17	+	
			4/18	+	
			4/19	—	
			4/20	—	

* 24-hour specimen taken on day of administration of mercury.

When double the amount, 2 gm. of the 50 per cent. ointment, was used as inunction, the amounts eliminated were relatively larger.

With the 33⅓ per cent. mercurial ointment, even when double the quantity was used, the elimination did not begin in appreciable amounts until the second day after inunction, and then in much less quantities than when the 50 per cent. ointment was given.

When the mercurial ointment was simply used by smearing on the skin, without rubbing, the amount eliminated was much less than when used as an inunction.

TABLE 2.—Unguentum Hydrargyri (50 Per Cent.) (2 gm. of Ointment Used)

Name and Age	Amount and Method of Administration of Mercury	Date of Administration	Date of 24-Hour Specimen	Amount of Mercury in Mg.	Remarks
D. H., 3 years	Unguentum hydrargyri (50%) 2 Gm. as inunction	7/31	7/31*	—	Congenital syphilis; Wassermann positive; female
			8/ 1	+	
			8/ 2	0.74	
			8/ 3	0.60	
			8/ 4	0.24	
			8/ 5	+	
			8/ 6	—	
	Same	8/ 7	8/ 7*	—	
			8/ 8	+	
			8/ 9	0.84	
			8/10	0.55	
			8/11	0.36	
			8/12	+	
			8/13	+	
			8/14	—	
			8/15	—	
	Unguentum hydrargyri (50%) 2 Gm. not as inunction	8/16	8/16*	—	
			8/17	+	
			8/18	0.34	
			8/19	0.14	
			8/20	+	
			8/21	—	
			8/22	—	
			8/23	—	

* 24-hour specimen taken on day of administration of mercury.

TABLE 3.—Unguentum Hydrargyri Dilutum (33 Per Cent.)

Name and Age	Amount and Method of Administration of Mercury	Date of Administration	Date of 24-Hour Specimen	Amount of Mercury in Mg.	Remarks
M. S., 3½ years	Unguentum hydrargyri dilution (33%) 2 Gm. as inunction	10/15	10/15*	—	Congenital syphilis; Wassermann positive; female
			10/16	0.20	
			10/17	+	
			10/18	+	
			10/19	—	
			10/20	+	
			10/21	—	
	Unguentum hygrargyri dilution (33%) 2 Gm. as inunction	10/22	10/22*	—	
			10/23	+	
			10/24	+	
			10/25	—	
			10/26	+	
			10/27	—	
			10/28	—	
			10/29	—	
A. E., 7 years	Unguentum hydrargyri dilution (33%) 2 Gm. as inunction	4/ 5	4/ 5*	—	Normal child; male
			4/ 6	0.10	
			4/ 7	+	
			4/ 8	+	
			4/ 9	+	
			4/10	+	
			4/11	—	
			4/12	—	
	Unguentum hydrargyri dilution (33%) 2 Gm. not as inunction	4/13	4/13*	—	
			4/14	+	
			4/15	+	
			4/16	—	
			4/17	—	
			4/18	+	
			4/19	—	
			4/20	—	
			4/21	—	

* 24-hour specimen taken on day of administration of mercury.

In the case of calomel ointment, it will be seen that the elimination is delayed, and the total quantity eliminated is much less than with the mercurial ointment, although two grams was used for each inunction.

With the mercurial salicylate in oil, used hypodermically, it will be seen that the maximum elimination is in the first twenty-four hours—smaller quantities continuing to be eliminated for six or seven days.

TABLE 4.—Calomel Ungt. (30 Per Cent.)

Name and Age	Amount and Method of Administration of Mercury	Date of Administration	Date of 24-Hour Specimen	Amount of Mercury in Mg.	Remarks
L. F., 5 years	30% calomel unguentum 2 Gm. as inunction	4/20	4/20*	—	Normal child; female
			4/21	—	
			4/22	+	
			4/23	0.12	
			4/24	+	
			4/25	—	
	Same as above	4/26	4/26*	—	
			4/27	—	
			4/28	+	
			4/29	0.24	
			4/30	+	
			5/ 1	—	
			5/ 2	—	
			5/ 3	—	
J. B,. 3 years	30% calomel unguentum 2 Gm. as inunction	8/15	8/15*	—	Congenital syphilis; Wassermann positive; female
			8/16	—	
			8/17	+	
			8/18	0.14	
			8/19	+	
			8/20	—	
			8/21	—	
			8/22	—	
	Same as above	8/23	8/23*	—	
			8/24	—	
			8/25	+	
			8/26	0.30	
			8/27	+	
			8/28	—	
			8/29	+	
			8/30	—	
	30% calomel unguentum 2 Gm. not as inunction	8/31	8/31*	—	
			9/ 1	+	
			9/ 2	+	
			9/ 3	—	
			9/ 4	+	
			9/ 5	—	
			9/ 6	—	
			9/ 7	—	
	30% calomel unguentum 2 Gm. not as inunction	9/ 8	9/ 8*	—	
			9/ 9	+	
			9/10	—	
			9/11	+	
			9/12	+	
			9/13	—	
			9/14	—	
			9/15	—	

* 24-hour specimen taken on day of administration of mercury.

The mercuric chlorid solutions used hypodermically continued to be eliminated in amounts not sufficient to be measured for six or seven days. In one case there was an appreciable amount of protein in the urine following its use, a point which we also observed in our previous experiments.

TABLE 5.—Mercury Salicylate in Oil (Intramuscular Injection)

Name and Age	Amount and Method of Administration of Mercury	Date of Administration	Date of 24-Hour Specimen	Amount of Mercury in Mg.	Remarks
J. F., 3½ years	Mercury salicylate (0.065 Gm.) in oil; intramuscular injection	4/ 5	4/ 5*	—	Normal child; male
			4/ 6	0.65	
			4/ 7	0.16	
			4/ 8	+	
			4/ 9	+	
			4/10	+	
			4/11	+	
			4/12	—	
			4/13	—	
	Same as above	4/14	4/14*	—	
			4/15	0.55	
			4/16	+	
			4/17	+	
			4/18	+	
			4/19	+	
			4/20	—	
			4/21	—	
M. L., 4½ years	Same as above	4/20	4/20*	—	Normal child; female
			4/21	0.46	
			4/22	+	
			3/23	+	
			4/24	+	
			4/25	+	
			4/26	—	
			4/27	+	
			4/28	—	
			4/29	—	
M. B., 6 years	Same as above	8/15	8/15*	—	Congenital syphilis; female
			8/16	0.60	
			8/17	0.18	
			8/18	+	
			8/19	+	
			8/20	+	
			8/21	+	
			8/22	+	
			8/23	—	
			8/24	—	

* 24-hour specimen taken on day of administration of mercury.

TABLE 6.—Mercuric Chlorid (Itramuscular Injection)

Name and Age	Amount and Method of Administration of Mercury	Date of Administration	Date of 24-Hour Specimen	Amount of Mercury in Mg.	Remarks
M. L., 4½ years	Mercuric bichlorid, 0.5 C.c. of 10% solution intramuscularly, i. e. 0.005 Gm. of mercury	4/ 5	4/ 5*	—	Normal child; female
			4/ 6	++	
			4/ 7	+	
			4/ 8	+	
			4/ 9	+	
			4/10	+	
			4/11	—	
			4/12	—	
			4/13	—	
	Same as above	4/14	4/14*	—	
			4/15	++	4/15, urine gave faint protein test
			4/16	+	
			4/17	+	
			4/18	+	
			4/19	—	
			4/20	—	
J. F., 3½ years	Mercuric bichlorid, 0.5 C.c. of 1% solution intramuscularly, i. e. 0.005 Gm. of mercury	4/20	4/20*	—	Normal child; male
			4/21	++	
			4/22	+	
			4/23	+	
			4/24	+	
			4/25	+	
			4/26	+	
			4/27	—	
			4/28	—	

* 24-hour specimen taken on day of administration of mercury.

TABLE 7.—Calomel (By Mouth)

Name and Age	Amount and Method of Administration of Mercury	Date of Adminis- tration	Date of 24-Hour Specimen	Amount of Mercury in Mg.	Remarks
M. F., 7 years	Calomel 1 grain by mouth	4/ 5	4/ 5*	—	Normal child; female
			4/ 6	+	
			4/ 7	+	
			4/ 8	+	
			4/ 9	+	
			4/10	+	
			4/11	—	
			4/12	—	
			4/13	—	
	Calomel 1 grain by mouth	4/14	4/14*	—	
			4/15	+	
			4/16	+	
			4/17	+	
			4/18	+	
			4/19	+	
			4/20	—	
M. B.,	Calomel ¼ grain by mouth every 4 hours for 4 doses	8/24	8/24*	—	Congenital syphilis; female
			8/25	+	
			8/26	+	
			8/27	+	
			8/28	+	
			8/29	+	
			8/36	+	

* 24-hour specimen taken on day of administration of mercury.

TABLE 8.—Gray Powder (By Mouth)

Name and Age	Amount and Method of Administration of Mercury	Date of Adminis- tration	Date of 24-Hour Specimen	Amount of Mercury in Mg.	Remarks
M. F., 7 years	Gray powder 3 grains by mouth every 4 hrs. for 4 doses	4/20	4/20*	—	Normal child; female
			4/21	±	
			4/22	+	
			4/23	+	
			4/24	—	
	Same as above	4/25	4/25*	—	
			4/26	+	
			4/27	—	4/26 Frequent stools; some tenesmus
			4/28	+	
			4/29	+	
			4/30	—	
			5/ 1	—	
M. S., 3½ years	Gray powder 3 grains by mouth	11/24	11/24*	—	Congenital syphilis; female
			11/25	±	
			11/26	—	
			11/27	—	
			11/28	—	
	Gray powder 3 grains once daily for 5 days	11/29	11/29*	—	
		11/30	11/30*	—	
		12/ 1	12/ 1*	+	
		12/ 2	12/ 2*	±	
		12/ 3	12/ 3*	±	
			12/ 4	+	
			12/ 5	—	
	Gray powder 3 grains every 4 hours for 4 doses	12/ 6	12/ 6*	—	
			12/ 7	—	
			12/ 8	0.14	
			12/ 9	+	
			12/10	—	
			12/11	—	
			12/12	—	
			12/13	—	
			12/14	—	

* 24-hour specimen taken on day of administration of mercury.

Calomel given by mouth (1 grain) either in one dose or divided doses, was eliminated in appreciable amounts although not sufficient to be measured for six or seven days.

Gray powder, although given in large doses, was eliminated to a very small extent and for a short period of time.

The practical deductions which may be drawn from this series of experiments are, therefore, as follows:

1. Mercurial ointment, 50 per cent., is to be preferred to the less concentrated forms and need not be repeated more often than twice weekly instead of daily. The quantity of mercury absorbed is much increased by friction.

2. Calomel ointment is absorbed but less rapidly and to a less extent than the mercurial ointment and should, therefore, be given in greater concentration.

3. The salicylate of mercury in oil should be given hypodermically twice weekly instead of once.

4. The mercuric chlorid, by hypodermic injections, although the dose is very small, continues to be eliminated for six or seven days. The fact, however, that its use frequently is followed by the appearance of protein in the urine should exclude it from the treatment of syphilis in children.

5. Calomel by the mouth is absorbed in small amounts, and continues to be eliminated for a considerable time so that it is probable that it would be sufficient to give it at intervals of several days, thus avoiding diarrhea.

6. Gray powder is absorbed to a small degree and eliminated rather rapidly so that large doses repeated daily would probably be necessary to maintain mercury in the circulation.

We shall continue our experiments and determine, if possible, whether the clinical results will bear out the observations made in these experiments. In one case (M. S.) of congenital syphilis, with marked keratitis, treated by inunctions of 50 per cent. mercurial ointment, once weekly, the clinical progress was apparently quite as satisfactory as in cases where daily inunctions were given.

STUDIES IN SPASMOPHILIA

I SPASMOPHILIA AND VITAMINS

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Although spasmophilia has been studied from almost every angle, and vitamins, at the present time very much in prominence, are known to have definite influence on the functions of the nervous system, no previous attempt, so far as I am aware, has been made to associate the one with the other.

By the term spasmophilia or spasmophilic diathesis, as used in this series of studies, is meant, as Langstein and Meyer recommend in their text book,[1] the latent condition in which there is hyperexcitability of the nervous system as shown by the electrical reactions or Chvostek's sign or both. For the active condition, manifesting convulsions, laryngospasm, carpopedal spasm or pylorospasm, the term tetany is reserved. Electrical reactions which are considered definitely characteristic of the spasmophilic diathesis are those in which the anodal opening contraction (AOC) is less than the anodal closing contraction (ACC) and is less than 5 ma. or the cathodal opening contraction (COC) is less than 5 ma. in infants of 1 year and under. No particular attention was paid to the Chvostek phenomenon as a pathognomonic sign. Unfortunately, there were no cases of tetany available, though one case (I.K.) which gave a cathodal opening contraction (COC) of less than 5 ma. had had convulsions and laryngospasm one month before this work was begun.[2]

As the electrical reactions permit of quantitative determination, any slight increase or decrease in the electrical irritabilty of the little patients could easily be checked up, following administration of the material under investigation. The infants were studied during the winter months (December, January and February) when spasmophilia is most apt to become manifest. They were under constant observation in an institution; the diets were prepared in a central diet kitchen and under absolute control. Three of the children studied were in well ventilated cubicles, and had been in those cubicles for some months prior to the investigation. The remaining children were in an open ward. No changes were made in the dietaries during the period if study.

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[1] Langstein and Meyer: Säuglingsernährung u. Säuglingsstoffwechsel, Wiesbaden, 1914, p. 347.

[2] The electrical reactions were tested with a Wappler wall plate apparatus, the indifferent electrode, being moistened with physiologic sodium chlorid solution, was placed on the abdomen, the Stintzig electrode, kept constantly moist with the solution, was applied to the peroneal nerve at the head of the fibula. The leg was held just above the malleoli, and the slightest twitch that could be felt, even though no movement of the foot or toes were visible, was taken as the minimum response or "end-point." An assistant held the indifferent electrode and moved the rheostat. The reactions were always done at the same time, in the morning. Very seldom did excessive crying or restlessness necessitate abandoning the tests.

WATER SOLUBLE B

The water-soluble vitamin was administered to infants showing spasmophilic reactions in three ways: (1) by oral administration of filtered autolyzed yeast; (2) by subcutaneous injection of the yeast filtrate boiled for one minute; (3) by subcutaneous injection of a watery solution of the alcoholic extract of ether-extracted wheat embryo. This solution was prepared by me after the method described by McCollum and Simmonds,[3] modified slightly to meet the necessity of having a sterile product. Chloroform, 0.2 per cent., was added as preservative, and the well stoppered bottles were kept in the refrigerator. Cultures of the finished product planted on blood-serum agar slants showed no growth after seventy-two hours incubation.

The yeast filtrate was prepared by mixing equal quantities of dry commercial yeast powder and water, incubating for twenty-four hours, and filtering. The antineuritic activity of the yeast filtrate and of the wheat embryo extract was tested on pigeons made polyneuritic by a polished rice diet. Five c.c. daily, of either, by mouth, was sufficient to effect a recovery from the polyneuritic state in from two to three days.

Yeast Filtrate.—Table 1 is typical of the results of oral administration of the yeast to four children. In no case was there an improvement in the electrical reactions.

Table 2 shows that yeast filtrate given subcutaneously had no influence on the electrical irritability. Although A. G. shows an apparent decreased irritability twenty-four hours after the injection, on the following day the reactions had returned to their former status. T. S. shows no change other than is encountered in the daily variations of the reactions.

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[3] McCollum, E. V., and Simmonds, N.: A study of the Dietary Essential Water-Soluble B, in Relation to Its Solubility and Stability Toward Reagents, J. Biol. Chem. **33**:55, 1918.

Wheat Solution.—Five infants were studied in this group, two of which (I. K. & T. S.) had previously received yeast filtrate. All were given two injections of 2 c.c. of the solution subcutaneously, then 4 c.c. were so given. In none were there any untoward effects; not even the slightest rise in temperature. Table 3 shows the results in one case, typical of the others. Another case in this group had been receiving yeast filtrate, 1 dram three times daily by mouth for five months previous to the wheat injections and showed the following spasmophilic reactions: CCC 0.6, ACC 2.0, AOC 1.6, COC> 5, which did not change after the administration of the wheat solution.

TABLE 1.—Oral Administration of Yeast

Name	Date	Therapy	Electrical Reactions			
			CCC	ACC	AOC	COC
I. K.	12/15/19	None	0.1	1.1	1.0	2.2
	12/16/19	None	0.1	1.6	1.1	2.2
2 mos.	12/17/19	1 dram t.i.d.	...	...	...	...
	12/18/19	1 dram t.i.d.	0.1	1.4	1.0	2.0
	12/20/19	1 dram t.i.d.	0.1	1.1	0.8	0.8
	12/21/19	2 drams t.i.d.	...	...	...	...
	12/27/19	2 drams t.i.d.	0.1	1.8	1.1	1.6
	1/ 6/20	2 drams t.i.d.	0.2	1.1	1.0	1.6

Diet: Eiweiss milk, with 2.5 per cent. fat, 24 ounces; orange juice, ½ ounce daily.

TABLE 2.—Subcutaneous Injection of Yeast Filtrate

Name	Date	Therapy	Electrical Reactions			
			CCC	ACC	AOC	COC
A. G.	12/6/ 19	None	1.0	3.2	2.2	>5
	12/9/ 19	None	0.6	3.0	2.4	>5
10 mos.	12/10/19	2 c.c.	...	...	...	...
	12/11/19	None	1.2	3.0	3.0	>5
	12/12/19	None	0.6	3.0	2.2	>5
	12/15/19	None	1.1	3.0	2.2	>5
T. S.	12/ 4/19	None	1.2	3.0	2.5	>5
	12/ 9/19	None	1.6	4.8	2.1	>5
7 mos.	12/ 9/19	2 c.c.	...	...	...	...
	12/10/19	None	1.1	4.0	2.0	>5
	12/12/19	None	1.6	2.8	2.8	>5
	12/27/19	None	1.2	2.2	1.8	>5

Diet: A. G., whole milk modification; orange juice, 1 ounce daily. T. S., Eiweiss milk with 2.5 per cent. fat; cereal; orange juice, ½ ounce daily.

Since none of these infants exhibited any permanent change in abnormal electrical irritability following administration of the water-soluble vitamin, it is safe to conclude that this abnormality was not due to a deficiency of this vitamin in their diet.

FAT SOLUBLE A

Electrical reactions were tested on four infants who had been on a dietary composed of 90 gm. of Krystalak (a highly skimmed, dried milk of less than 0.2 per cent. fat content), 30 gm. cane sugar, 15 c.c.

orange juice, 30 c.c. autolyzed yeast filtrate, 30 c.c. cotten seed oil and amounts of cream of wheat suitable to their ages, for a period of eight months. They are the infants studied by Hess and Unger[4] from the point of view of rickets and the fat-soluble vitamin. It will be noted that their dietary is as free from this vitamin as is ever obtained under the most severe clinical conditions, though otherwise entirely adequate. The electrical reactions were:

	CCC	ACC	AOC	COC
S. M.	0.6	2.0	1.6	> 5
C. M.	2.6	3.0	> 5	> 5
R. S.	1.8	2.2	> 5	> 5
E. L.	2.8	3.0	> 5	> 5

With one exception, the reactions are entirely normal. As none showed any signs or symptoms of spasmophilia, the conclusion is justified that a minimal fat-soluble dietary component is not concerned in the etiology of the spasmophilic diathesis.

TABLE 3.—Subcutaneous Injection of Wheat Solution

Name	Date	Therapy	Electrical Reactions			
			CCC	ACC	AOC	COC
I. K.	1/27/20	None	0.4	1.2	1.0	2.2
	2/ 3/20	None	0.2	0.8	0.6	1.0
4 mos.	2/ 8/20	2 c.c.	...	...	...	...
	2/ 8/20	None	0.2	1.2	1.0	1.8
	2/10/20	2 c.c.	...	...	...	...
	2/11/20	None	0.3	1.2	1.0	2.5
	2/12/20	4 c.c.	...	...	...	...
	2/13/20	None	0.6	1.4	1.1	2.0
	2/14/20	4 c.c.	...	...	...	...
	2/27/20	None	0.5	1.4	1.1	1.8

Diet: Eiweiss milk, with 2.5 per cent. fat, 28 ounces; yeast filtrate, 2 drams, three times daily; orange juice, ½ ounce daily.

ANTISCORBUTIC VITAMIN

Opportunity presented itself of testing the electrical irritability in two cases of active infantile scurvy. Both patients showed the classical picture of bleeding gums, pseudoparalysis of the legs, the cardiorespiratory syndrome, capillary resistance test of Hess and one had subcutaneous and subperiosteal hemorrhages about the knee joint. Their electrical reactions were as follows:

	CCC	ACC	AOC	COC
S. K.	1.6	> 5	> 5	> 5
S. F.	2.0	> 5	> 5	> 5

These reactions show an irritability unusually low for children of their ages, both being 2 years old.

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[4] Hess, A. F., and Unger, L. J.: The Clinical Rôle of the Fat-Soluble Vitamin; Its Relation to Rickets, J. A. M. A. **74**:218 (Jan. 24) 1920.

DISCUSSION

In view of certain similarities between beriberi in its early stages and active tetany, it was thought that a deficiency in the diet of the antineuritic vitamin might play a rôle in the causation of spasmophilia. In both conditions the nervous system is involved, giving rise to such symptoms as hoarseness and laryngospasm. The end results of the two conditions, on the other hand, is entirely different, beriberi being rapidly fatal if not treated, spasmophilia rarely (per se) terminating in death.

The study here presented serves only to rule out the possible relation between the heightened electrical irritability—so-called "spasmophilic reactions"—and any deficiency in the diet of the water-soluble vitamin. This is all the more striking in view of the antineuritic content of orange juice, as shown by Osborne and Mendel[5] and more recently by Byfield and Daniels,[6] when we remember that the infants studied in this group were all receiving a liberal allowance of orange juice in their dietary, yet they showed the electrical changes characteristic of spasmophilia.

The very frequent association of spasmophilia and rickets, and the prominence which has recently been given to the fat-soluble factor in connection with rickets, serves only to add interest to the normal electrical reactions obtained in those children whose diet contained a minimal quantity of this factor.

No further comment is necessary on the reactions found in the scorbutic cases.

CONCLUSIONS

The evidence here presented shows that increased electrical irritability—so-called "spasmophilic reactions"—is not dependent on a deficiency in the diet of the water-soluble vitamin or of the other two known food accessory factors.

I wish to express my gratitude to Dr. Alfred Hess of New York for his many suggestions, advice and stimulating criticism.

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[5] Osborne, T. B., and Mendel, L. B.: Do Fruits Contain Water-Soluble Vitamin? Proc. Soc. Exper. Biol. & Med. **17**:46 (Nov. 19) 1919.

[6] Byfield, A. H., and Daniels, A. L.: The Antineuritic and Growth Stimulating Properties of Orange Juice, Am. J. Dis. Child. **19**:349 (May) 1920.

CLINICAL DEPARTMENT

A CASE OF PRIAPISM RESULTING FROM RAPIDLY SPREADING MYXOSARCOMA WITH GENERALIZED METASTASES*

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REPORT OF CASE

Raymond G. (Case 5140), schoolboy, aged 9 years, entered the pediatric service of the University Hospital March 4, 1920. His chief complaints were lameness and stiffness of the back and neck; stiffness and difficulty in moving the left upper extremity; priapism, which had been persistent for about three weeks; some difficulty in swallowing and in articulating his words because of stiffness of the face muscles and inability to open his mouth freely; disturbed vision; headache situated in the right supraorbital region; difficulty in starting micturition, but no pain.

Family History.—The father, who is a laborer, had an accident six years ago last June: "Some ribs were broken and also his collar bone in two places." December, 1919, he had three marked hemorrhages in twenty-four hours which were thought to have been pulmonary. None since. "He is just as well now as he was before he had the hemorrhages." Mother's father and sister are said to have died of pulmonary tuberculosis. Mother died of what was called typhoid pneumonia. The history seems to show that shortly after Raymond's birth, there was strong suspicion that she was tuberculous. About three months after she was thought to be cured, she developed this fever, "typhoid pneumonia," which continued six weeks, and then she died. Raymond was the first child, born two years after marriage.

Past History.—Patient had measles when 4 or 5 years of age. He had no other infectious diseases. He was a strong baby. As he developed he became "moody," subject to dreamy spells; he would go off by himself and think and seem to be in a dream. He started in school at the age of 6 and advanced to the fourth grade. He always complained a great deal of headaches, cried easily and was hard to cheer up. He began to complain of his neck and back being stiff and aching about a year before entering the hospital. He was better in the warm weather. His "worst time seemed to be between January and May" so that when the present trouble began it was thought to be a recurrence of the same thing. There is a history of frequent earaches.

Injuries: He had been definitely hurt on two occasions, once when he was pushed off the schoolhouse platform, falling three feet, face down; "cried all afternoon saying his back hurt," and once when he had the coasting accident which has been thought to have played a great part in the development of his present illness.

Present Illness.—About Dec. 28, 1919, while sliding down hill, Raymond had one hand on each runner of the front of his sled, one knee on the back of the sled; with the other foot he was starting the sled down hill when his playmate jumped on his back. He went home screaming with pain in his back and his back was lame for several days. He returned to school. It was thought that after the accident his appetite became poor; that he was easily annoyed; the children playing seemed to bother him; while he played at times, he was not as playful as before. (This detailed account of the accident is given because of its possible connection with the development of the primary growth. Some have taken the view that it would be impossible to hurt the genital organs by such an accident, on the other hand, it is possible that he may have fallen astride the sled and thus injured the scrotum or perineum. There is no history of pain in this region.)

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* From the Department of Pediatrics and Infectious Diseases, University of Michigan.

* Read before the American Pediatric Society, Highland Park, Ill., May 31, June 1 and 2, 1920.

About the middle of January, 1920, he began to complain of pain and aching in his back. He again became stiff and was unable to bend over or to either side or to twist himself. His whole spine was rigid. Severe headaches developed, keeping him awake at night. He also, at this time, complained of dull pain in his knees which has occasioned a limp in his walk, more marked on the right side. About three weeks before entrance to the hospital, priapism developed and has been continuous. There is difficulty in starting urination; this is accomplished twice daily without pain or other abnormality. Soon after the development of priapism he noticed that he was unable to see objects placed on the left of him and that his right eye turned in. The speech and swallowing defect date from the last fall when his jaws began to get stiff. He talks through his teeth without moving his jaw and he swallows with a definite impediment, choosing liquid foods. Difficulty in moving the left upper extremity is of recent occurrence. At times it is almost impossible for him to raise the left arm above the head.

Physical Examination on Entrance.—Slender prominent frame, wasted musculature; practically no panniculus; no edema. There is no play of the facial muscles. The jaw is stiff. The teeth open only 1.5 cm.; if an attempt is made to open the mouth it induces pain. The teeth are carious; *fetor exore.* The patient's body is stiff. The spine cannot be bent and the back muscles are stiff, like a board. He turns his head slightly from side to side, but this is largely accomplished by moving the body with it. He cannot move his head up and down. When he arises to the sitting position the head, neck and body are almost perfectly rigid. If any attempt is made to bend his back in any direction he cries out with pain. He has difficulty in raising the left upper extremity above the head. The other extremities show no limitation of motion. When the thighs are rotated there is pain in the hips. An attempt to rotate the legs causes pain in the knees. Grip in both hands is fair. The patella, ankle and elbow reflexes are not obtained. Babinski is negative; Oppenheim and Brudzinski cannot be obtained. (The knee jerks have been tested on many occasions. At one time they were thought to be present.) Pupils are equal and react promptly to light, slowly in accommodation. There is paralysis of the left external rectus. The patient is unable to rotate the left eye outward. There is no nystagmus. The vision in the right eye is definitely impaired; persons are seen as mere shadows; unable to count fingers or coins. There is definite tenderness on pressure above the right eye. There are no tremors. The other joints are prominent but show no abnormalities. The skin is pale and dry. There is considerable lanugo hair on the face and a slight amount of pubic hair. The glands are practically negative. The inguinal glands are felt, small. When the patient walks he does so with great care, standing with his body perfectly stiff and favoring the right extremity. When he attempts to pick up an object from the floor he bends at the knees and keeps the back straight.

The head is symmetrical and presents no abnormal prominences. Aside from the facies it is negative.

Thorax: Juvenile type. Pressure over the ribs at several points shows tenderness, otherwise negative.

Lungs: Percussion negative. Auscultation shows nothing definite. Spinal dullness extends only to the first dorsal. No d'Espine.

Heart: Negative.

Abdomen: Liver edge at costal margin. Kidneys and spleen not felt. The muscles are held very tense. No hernias.

Genitalia: Priapism is marked, continuous and painful if manipulated (Fig. 1). The prepuce can be retracted. No smegma. Both testicles felt in the scrotum.

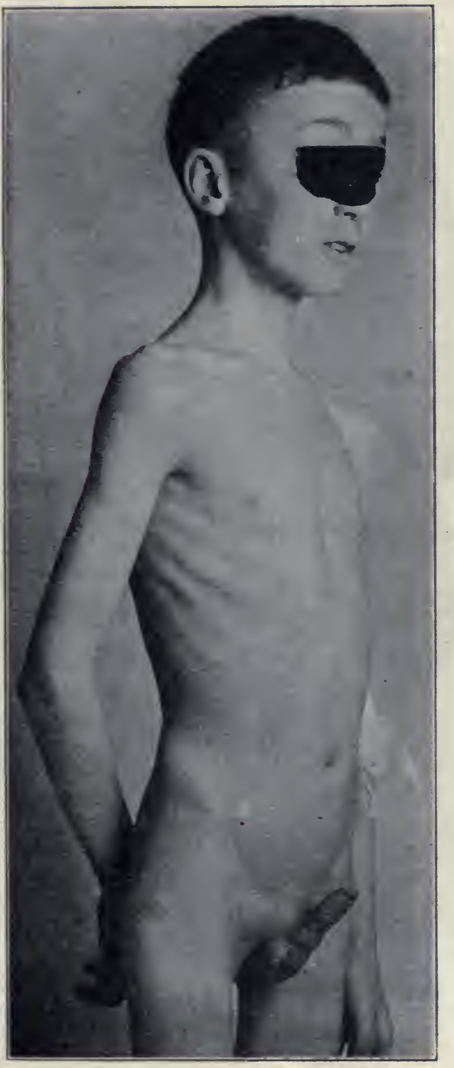

Fig. 1.—Taken soon after the tumor in the scrotum was first visible. The stiffness of back, neck and face muscles is evident; fixation of the jaw and priapism are marked.

Laboratory Findings.—Urine: The urine was examined on many occasions. Aside from high specific gravity it was negative. Urea and other biochemical tests not done.

Blood: March 4, 1920.—Red cells, 5,150,000; white cells, 12,000. Differential count shows polymorphonuclears, 71.2 per cent.; basophils, 4.1 per cent.; large lymphocytes, 17.1 per cent.; small lymphocytes, 7.6 per cent.

March 9, 1920.—Leukocytes, 18,000; hemoglobin, 62 per cent. Arneth count shows slight shifting to the left as follows: Mononuclear, 36 per cent.; binuclear, 35 per cent.; trinuclear, 23 per cent.; quadrinuclear, 5 per cent.; quinqinuclear, 1 per cent.

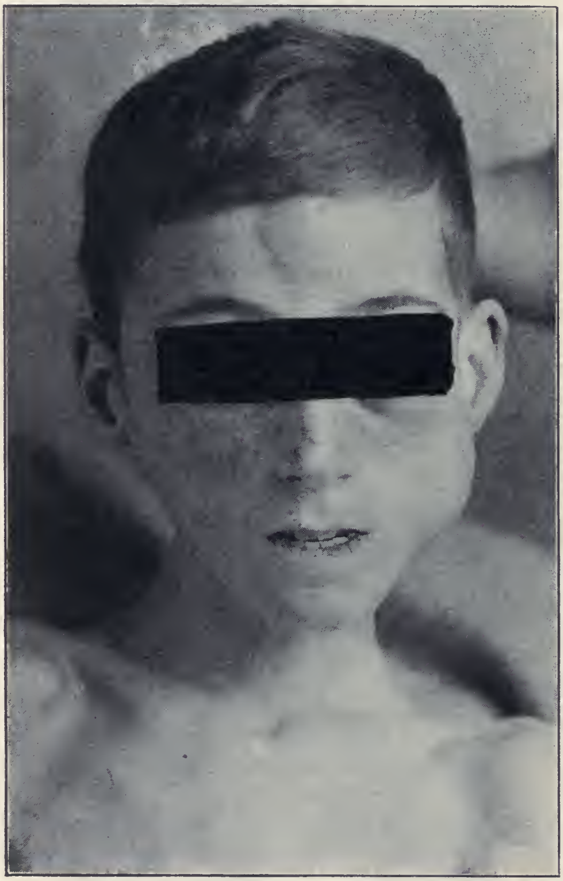

Fig. 2.—Showing the marked increase in size of the mass on the left jaw, the frontal nodule, and the nodule to the right of the sternum and the eye changes.

March 10,—Red cells, 4,400,000; white cells, 20,000.

Spinal Fluid: March 7.—Lumbar puncture in the sitting position; 4 c.c. of clear fluid ,came away under normal pressure. No more would flow out. Ten cells per field. Definite clouding with carbolic test. Otherwise negative.

March 9.—Lumbar puncture sitting position; 7 c.c. perfectly clear fluid under normal pressure was obtained. Cell count seven per field. Saturated ammonium sulphate negative. Phenol gives a definite cloud, positive. Fehling's test shows a reducing substance present. Collodial gold, 0112210000.

Wassermann: Blood and spinal fluid Wassermann negative.

Tuberculin Test: Repeated von Pirquet tests have been negative with 25 and 50 per cent. solutions.

Reports from Special Clinics.—Otolaryngology: Septic tonsils. Small mass of adenoids. Nasal cavities negative. No evidence of sinus disease. Ears negative.

Opthalmology: Optic neuritis, O. D., paralysis of left external rectus. Pupil, O. S., dilated more under mydriatic than O. D., indicating partial paralysis of the ciliary muscles O. S.

Syphilology: Clinical examination for hereditary syphilis entirely negative.

Roentgenology: Stereoroentgenogram of the head for sinuses shows all sinuses air containing, negative. The sella is normal in every respect. Roentgenogram of jaw is negative. Roentgenogram of spine, shows it to be perfectly normal.

Clinical Notes.—Temperature: Patient had an irregular temperature without any definite type, varying between normal and 101 F. (a few times it reached 102) until March 24, after which it remained practically normal until death, April 8, 1920.

The pulse rate varied between 100 and 140; otherwise nothing remarkable.

March 5.—A roentgen-ray examination suggests some involvement of the left upper chest (there was some suspicion of involvement of this part of the chest on the entrance examination). The spine is entirely negative.

March 8.—Priapism continues. There is a definite small mass in the scrotum posterior to the right testicle. The right testicle is free. The left is felt but is difficult to outline. There is a well circumscribed mass at the angle of the left jaw about the size of a hickory nut. It is fairly firm. The patient is unable to open his mouth more than 1 cm. He has difficulty in pronouncing words. There is nystagmus of the right eye when it is fixed on an object to the left. Knee jerks cannot be obtained.

Provisional Diagnosis.—Malignant tumor in the scrotum with metastasis in bone and cerebrum. The latter probably responsible for the eye signs. The tumor is probably a teratoma.

March 9.—Patient says he has to bear down very hard to start his urine, but there is no pain. The urine is clear.

March 11.—Patient is not as bright as a week ago. Return of his aunt caused no emotional reaction; he made no response to her salutation. He complains of persistent frontal headaches. There is pain on pressure over both supraorbital nerves during the past few days.

Metastases: Swelling half an inch in diameter has developed in the center of the forehead. This is firm and circumscribed. The swelling at the angle of the left jaw (Fig. 2) is increasing and is still firm. There is pain on pressure over the third right costosternal articulation and at the sternoclavicular joint. Patient complains of his back and calf muscles being sore. He seems to walk a little better.

March 10.—A large nodule is felt over the left occipital bone 3 cm. in diameter, firm, painful, elevated 0.5 cm. above the skull.

March 18.—The tumor mass in the scrotum is increasing in size. The jaw mass, which receded a bit after the roentgen ray was used, is larger. The teeth cannot be separated as well as before. It is difficult to understand what the patient says.

March 21.—Forehead nodule is 2 cm. in diameter. A smaller nodule has appeared on the top of the head, hard and attached to the bone, slightly tender to pressure. The occipital nodule is larger, very tender. The jaw nodule continues to enlarge; is more irregular. A similar nodule is developing on the right jaw in the same location. Scrotal mass is larger and is rapidly extending toward the anus. The right inguinal glands are now as large as small almonds. The patient was transferred to surgery service for biopsy.

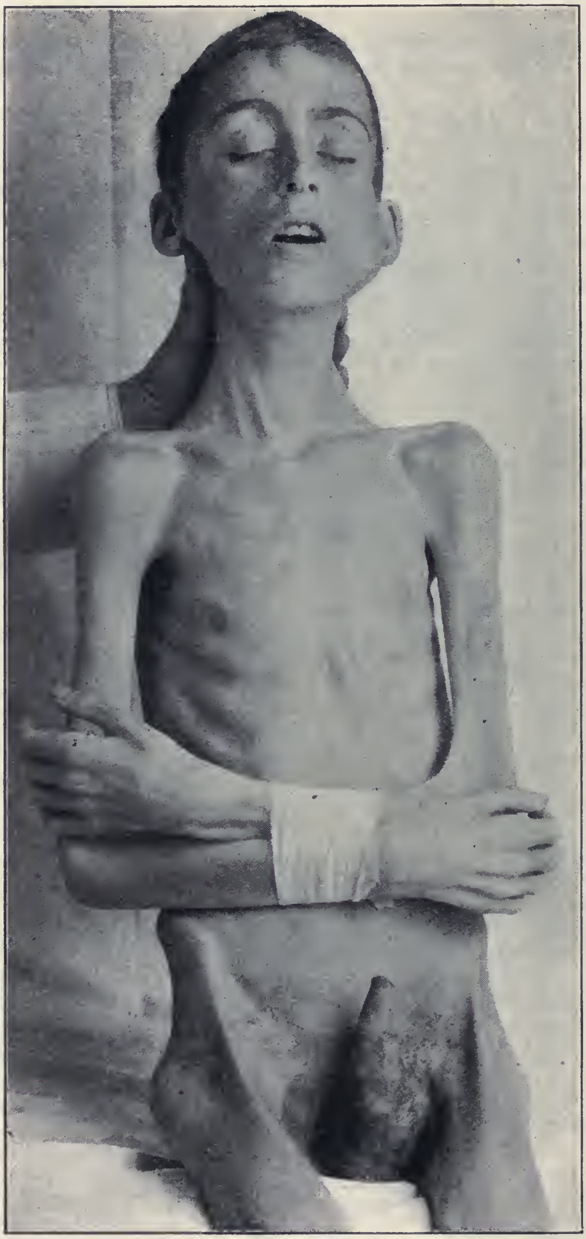

Fig. 3.—Taken soon after death, showing the nodule recently developed on the right jaw and the extent of the scrotal growth.

March 23.—Tumor mass in the scrotum has grown very rapidly and is very hard. Both testes can be felt separate from the mass. A mass in the right inguinal region the size of a hickory nut is now felt (Figs. 3 and 4).

April 1.—A friction rub over the chest on both sides is heard, more noticeable on the right side than on the left. No change in the whispered or spoken voice. There is a small nodule on the third right costal cartilage near the sternum, the size of a large pea. The other nodules are all increasing in size and a new one is developing in the right temporal region which does not seem to be as hard as the others. The tumor mass in the scrotum is extending farther down, and is also beginning to extend up into the body of the penis. Mastication is now almost impossible. Patient is losing weight rapidly. The heart is negative. Patient complains of being short of breath. The chest is full of ronchi, particularly on the right side in the axillary region. No definite râles or dulness can be made out. The patient cannot be turned for examination of the back because of great distress. There is still pain on manipulation of the penis and the masses are more marked. Small nodules have developed up to the end of the prepuce.

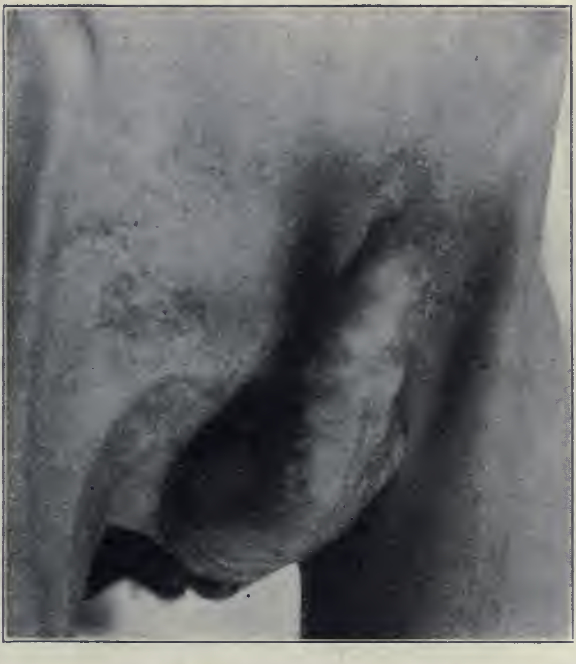

Fig. 4.—A closer view to show the nodular masses along the penis and prepuce.

In general, it may be said that the skull is full of nodules, altogether, large and small, seven are counted. The first one described over the left occipital bone is 4 cm. in diameter; the one over the forehead is 3 cm. in diameter. They project fully 1 cm. above the skull (Figs. 5 and 6).

April 2.—The process can be seen to advance daily. Nodules about the size of peas can be seen to have developed since yesterday. The left testicle seems to be lost in the tumor mass which is very much larger in all directions. Feeding by gavage.

April 7.—There are tubercles all along the penis up to the glans. A nodule has developed on the right superior maxillary, just external to the right orbit.

April 8.—Biopsy Report: Dr. Warthin reports the tissue as an alveolar myxosarcoma, congenital type, probably primary in the bladder.

The patient is slightly cyanotic this morning. The cyanosis extends down over the shoulders. The heart sounds are masked by the ronchi. The liver and spleen cannot be felt.

The patient died suddenly at noon.

SUMMARY

This is a case of a rapidly developing tumor in the scrotum associated with what I believe to be multiple metastatic growths in the skeletal structures, intracranial changes, indefinite intrathoracic changes particularly on the left side, not involving the heart; with a history of injury which, however, occurred, apparently, after he first complained of back stiffness, but which may have had an influence in the process. We are thus far unable to determine the cause of the painful rigidity of the back and neck muscles. The patient seemed to be holding himself for fear of being hurt. The boardlike stiffness reminds one of that described by Escherich in his cases of pseudotetanus. This condition, however, is at once ruled out.

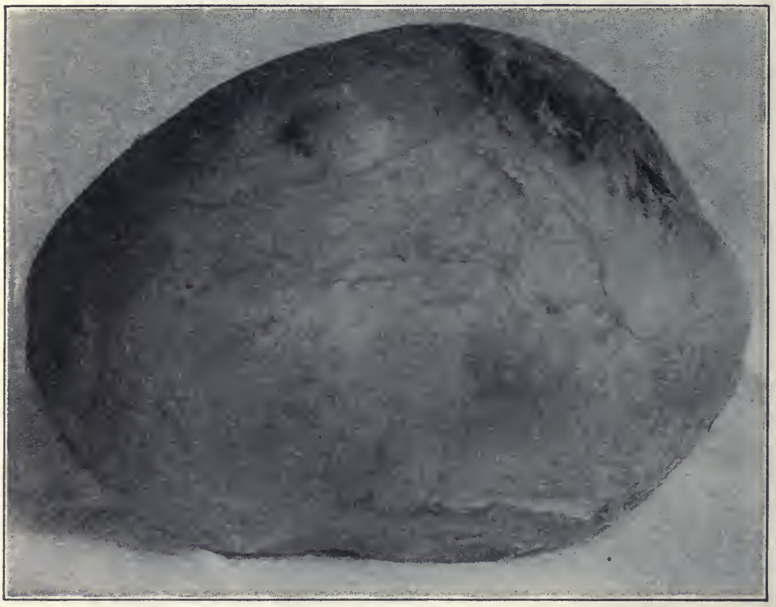

Fig. 5.—Skull cap outer surface.

Instead of more than one process being at work to induce the different groups of symptoms, I believe the entire process is due to a malignant tumor with bone and visceral metastases. I have seen a number of malignant tumors in children in the clinic. Because of bone metastases we made the tentative diagnosis of malignant teratoma. Dr. Cabot concurred in the idea of malignant tumor and Dr. Warthin, before the child's death, concurred in the probability of its being a teratoma.

NECROPSY PROTOCOL

The following notes are extracted from Dr. A. S. Warthin's necropsy records, made April 8, 1920.

Gross Findings.—There is a great abundance of lanugo hair over the face and upper extremities, nodular masses on the scalp and angles of both jaws, in the center of the forehead, on the costal cartilage at the junction of the third rib. Nodules were also found on the anterior surface of the sacrum. The bodies of the vertebrae were all involved, nodules being found on either side along the entire course of the spine. In the upper thoracic region there was a marked deformity bringing about anterior projection of the bodies of the thoracic vertebrae just behind the esophagus at the suprathoracic straits (this in part accounts for the difficulty in swallowing). The bodies of the vertebrae were infiltrated with the growth, so much so that they could be easily picked to pieces. The masses in the scalp were semi-elastic. The floor of the cranium was also involved in the tumor growth. There was a large soft metastasis involving the roof of the orbit and cavernous sinus on both sides, particularly the right.

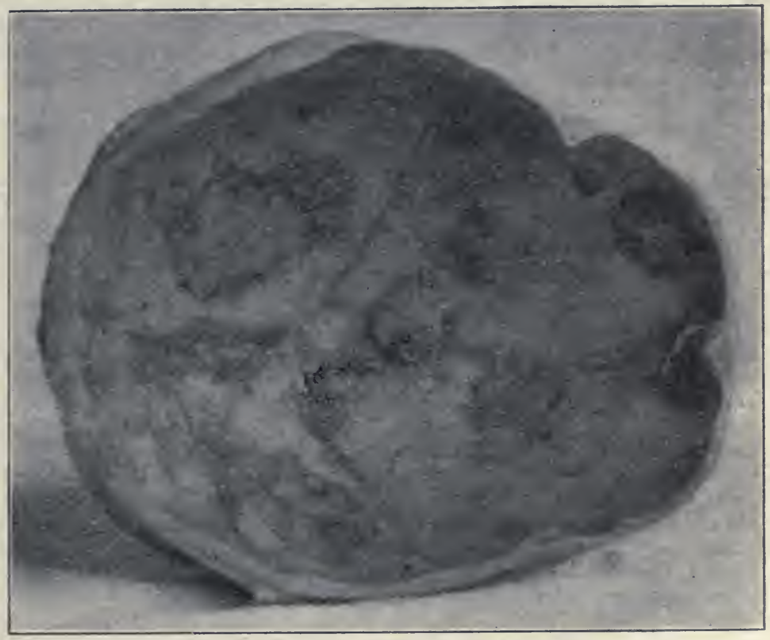

Fig. 6.—Skull cap inner surface.

Heart: The heart was negative, excepting for pallor of the heart muscles.

Lungs: The left lung was filled with metastases. The right was adherent. Both plueral cavities contained fluid. The fluid was slightly cloudy on the right side. Some of the nodules on the surface of the left lung were from 1.5 to 2 cm. in diameter and elevated 0.5 cm. above the surface; light yellowish in color and resembling a button. One of these was umbilicated. The same buttonlike nodules were found on the upper surface of the diaphragm. The bronchial glands on the left were hyperplastic and edematous. No metastases. On the right they were entirely replaced by metastases the size of hickory nuts. When these were cut through they appeared soft, cheesy and yellow.

Stomach: Negative.

Pancreas: Negative.

Liver: Negative. One area showed a diffuse infiltration.

Spleen: Negative.

Intestines: Negative.

Genitals: The testicles were pushed up into the canal by the scrotal tumor and were not involved in the growth. The bones of the pelvis showed only secondary processes. The bladder showed no growth; the thickening in the wall was all in the subserosa. The primary growth was found in the prostate; the entire gland being replaced by the new growth. The urethra was surrounded by a soft, mushy, purulentlike growth. The penis was almost entirely replaced by the nodular masses varying in size from a buckshot to a pea.

Brain: The central longitudinal sinus contains metastatic nodules in its anterior portion. The circle is negative. The basal meninges are negative. The arachnoid shows irregular thickening between the convolutions. The meninges strip with difficulty, markedly edematous. There are adhesions between the arachnoid and the cortex. The ventricles are negative. The brain substance shows anemia but no metastases. The cerebellum, medulla and cerebral cord were edematous. The hypophysis was atrophic. The sella was nearly filled with neoplasm. The brain weighed 1,330 gm.

Microscopic Findings.—Brain: Congestion and edema. No metastases in brain substance.

Cranium: Metastases in scalp, cranium and floor of skull. Show a picture of round cell alveolar sarcoma.

Vertebrae: All metastases show the picture of an alveolar round cell sarcoma.

Heart: Simple atrophy. Fibroid atrophy. No neoplasm.

Clot from Heart: A laminated mixed clot containing nests of tumor cells.

Aorta: Slight fatty degeneration of the intima.

Lungs: Purulent bronchopneumonia with numerous streptococci colonies. Numerous metastases, some of round cell and others of an oat-seed spindle cell histoid sarcoma. The centers of the metastatic growths show marked tendency to caseous necrosis.

Bronchial Lymph Glands: Show metastases. Calcareous healed tubercle.

Prevertebral and Mesenteric Nodes: All filled with metastases. Some of the large mesenteric vessels contain masses of tumor cells. The prevertebral ganglia and the roots of the spinal nerves are surrounded by masses of tumor cells.

Thymus: Many large corpuscles of Hassal.

Thyroid: Abundant colloid. No metastases found.

Tonsil: Moderate hyperplastic tonsillitis.

Spleen: Simple atrophy. Congestion. Thrombosis of splenic vessels. Small metastases in some of the splenic follicles.

Suprarenals: Atrophy. Slight lipoidosis.

Kidneys: Slight cloudy swelling. Congestion.

Pancreas: No metastases.

Liver: Slight atrophy. Cellular infiltration of some of the periportal islands.

Stomach: Simple atrophic catarrh.

Colon: Slight mucous colitis.

Appendix: Negative.

Small Intestine: Slight catarrhal enteritis.

Urinary Bladder: Slight chronic cystitis. Diffuse infiltration of the wall with neoplasm.

Prostate: No prostatic tissue can be recognized. Completely replaced by alveolar round cell sarcoma.

Penis: Corpora cavernosa and corpus spongiosum infiltrated with round cell alveolar sarcoma; in many places by cells of an oval or oat-seed shape. Numerous areas of simple caseous necrosis.

Hemolymph Nodes: Numerous phagocytes containing hemosiderin in sinuses.

Final Pathological Diagnosis.—Alveolar oat-seed sarcoma, primarily a myxosarcoma, arising in region of prostate. Infiltration of cavernous spaces of penis with chronic priapism; erosion of pubic bone; infiltration of bladder wall; multiple metastases in skull, vertebrae, ribs, sternum, lungs, pleura, diaphragm, spleen and lymph nodes; infiltration of cranial and spinal nerves and sympathetic ganglia; free ball thrombi containing neoplasm cells in right heart; thrombosis of retroperitoneal and splenic vessels with tumor cell embolism; terminal acute bronchopneumonia; general marasmus; fibroid atrophy of thymus; hemosiderosis of lymph nodes; postmortem pseudomelanosis.

The stiffness and sensitiveness of the back are now explained by the necropsy findings along the course of the spinal column.

PROGRESS IN PEDIATRICS

A REVIEW OF THE LITERATURE OF 1919 ON THE GENITO-URINARY DISEASES OF CHILDREN

LEWIS WEBB HILL, M.D.
BOSTON

MALIGNANT TUMORS OF THE KIDNEY

Rossi[1] reviews the literature on this subject and reports three cases. There are only a few instances of operative cures on record, and recurrence is frequent, but an operation is the only means of possible relief, and the success in one of his cases justifies high hopes with radical intervention. In one of the cases on record, the tumor compressed the ureter from the other kidney, inducing hydronephrosis in this, and the urine from the sound kidney found its outlet through the sarcomatous kidney, the ureter from this being still permeable. Enlargement of the kidney is always the first symptom of the malignant disease in children. Hematuria is not always present, and pain is an unreliable element in the differential diagnosis. His first two cases were in children 2 years of age; one was inoperable, but the other child recovered and seems still in perfect health, eight years since the nephrectomy. The tumor was a round cell sarcoma, weighing 600 gm. The child had been apparently healthly until two months before the operation. He removed the tumor likewise in the third patient, a girl aged 8, and the child seems well, but the interval since has been too short for the ultimate outcome to be known. In deciding whether the tumor was in the kidney or spleen, he found instructive the appearance of a zone of resonance in front of the tumor when the intestine was inflated. This resonance is not encountered with a tumor in the spleen. A tumor in the intestine or mesentery generally runs a very rapid course, entailing cachexia early. Such tumors are also extremely movable, while a tumor in the pancreas is not movable. A conglomerate of tuberculous glands might prove misleading, but almost invariably tumefied glands or other symptoms elsewhere would give the clue. A congenital cystic kidney may also simulate a malignant tumor. In a case of this kind, a hard elastic tumor in the kidney region, movable with respiration but without fremitus or resonance in front, without eosinophilia, the blood pictures and urine normal, was shown by exploratory puncture to be a cystic tumor implanted on the large right kidney. The left kidney was missing. Uneventful recovery followed the excision of the tumor.

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[1] Riv. di clin. Pediat. **16:**12 (Dec.) 1918; abstr., J. A. M. A. **72:**834 (March 22) 1919.

THE SUPRARENALS

It is gradually being realized that the suprarenals, as well as the kidneys, may be the seat of pathologic changes in infectious diseases, and that such changes are not at all uncommon. McCarrison[2] studied the effect of a scorbutic diet on the suprarenals of guinea-pigs which were fed on crushed oats and autoclaved milk. The naked eye changes consist in enlargement of the suprarenals with increase in their weight and in congestion. The weight of the suprarenals of guinea-pigs dying of scurvy is approximately double that of healthy guinea-pigs. The microscopic changes consist in a hemorrhagic infiltration and disintegration of the cellular elements of the cortex and medulla. These changes occur in animals who may show no clinical evidence of scurvy during life. They are to be regarded as prescorbutic in character. In spite of the fact that the weight of the organs is twice as great, the total quantity of epinephrin contained in the glands is less than half that in those of healthy guinea-pigs.

Byrne[3] performed a necropsy on a number of war prisoners who died of starvation. He says "While working as a prisoner of war behind the German lines in a prison hospital (lager) it fell to my lot to carry out several necropsies on British and Allied soldiers who died in the lager. Many batches of prisoners arrived from neighboring working parties where they had been systematically underfed, and had been worked until they were physically prostrated. From each batch some members died a very short time after admission. I was greatly impressed by the size of the suprarenals in these cases. In a series of eight deaths from underfeeding the suprarenals were definitely enlarged, almost half again as large as normal. Macroscopically, the enlargement seemed to involve mostly the cortex. Apparently the suprarenals had hypertrophied to counteract the low blood pressure produced by starvation."

Comby,[4] quoting an article of Friederichsen's,[5] says that hemorrhage into the suprarenals is not rare in children. It appears as a fairly definite disease. It is usually bilateral, acute and rapidly fatal. In new-born babies, traumatism, an umbilical infection, or the sudden changes in the character of the circulation, might be causes; in older babies, infection of some sort is probably the cause. Fever was present in all cases. Experimentally, it has been found that injection of various organisms into guinea-pigs may produce suprarenal hemorrhage, also the author saw it in a case of scarlet fever. The most striking clinical appearance about the children is the inertia and asthenia.

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[2] Brit. M. J. **2**:200 (Aug. 16) 1919.
[3] Brit. M. J. **2**:135 (Aug. 2) 1919.
[4] Arch. de med. d. enf. **21**:651 (Dec.) 1918.
[5] Ugesk. f. Læger **79**:446 (March) 1917.

Hill[6] reports a case of acute nephritis in which a very low blood pressure (60) was accompanied by marked asthenia. The blood pressure became lower, and the asthenia more marked. A few days before death the blood pressure was so low that it could not be recorded. No necropsy was made, but the author believes that the suprarenals were involved in the same inflammatory condition that the kidneys were, and that this was the cause of death.

Cowie and Beaven[7] draw attention to the fact that the French school assumes the presence of suprarenal involvement in many of the acute infections, and believe that this complication follows certain infections as regularly as nephritis follows scarlet fever. Since three very prominent symptoms in influenza and influenzal pneumonia are asthenia, prostration and a low blood pressure, they are of the opinion that there is suprarenal damage in many of the cases. At necropsy they found no hemorrhages or other inflammatory changes in the suprarenals, but merely a hypoplasia. They tried epinephrin injections to combat the low blood pressure and asthenia, but conclude that they are of little value.

ENURESIS

Enuresis is much like whooping cough; dozens of remedies have been used to control it, none of which are very efficacious. If there were any really good treatment of enuresis, everybody would be using it, instead of employing the many widely varying methods that are used.

Provinciali[8] reviews the various theories that have been advanced to explain enuresis, and states that in eight out of ten children of this category roentgen-ray examination revealed anomalies in the lumbosacral portion of the spine. In only two were these parts of normal aspect. The children with these anomalies did not show any other appreciable signs of degeneracy. As children usually outgrow the enuresis in time, he urges roentgen-ray examination of their spines to see if it might not be possible to detect the nature of the anatomic changes which put an end to the enuresis.

Cameron[9] believes that most of the ordinary causes alleged to be important in enuresis have little to do with it (adenoids, phimosis, etc.). It is mostly a neurosis. He believes that suggestion is very important;

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[6] Am. J. Dis. Child. **17**:270 (April) 1919.

[7] Arch. Int. Med. **24**:78 (July) 1919.

[8] Pediatria **27**:567 (Sept.) 1919; abstr., J. A. M. A. **73**:1317 (Oct. 25) 1919.

[9] Practitioner **100**:112, 1918.

the parents make so much of the enuresis that the child just naturally wets. Usually when the child is sent to the hospital it stops to wet, because nobody pays any attention to it. Enuresis is explicable if we assume that the want of control is due at the beginning to autosuggestion, or to the unwise attitude adopted toward the fault by the nurses and parents, and later kept up by the sense of shame and the mental distress involved.

As regards treatment, the procedures that have been advised may be divided into five groups.

1. Operative: Adenoid operation and circumcision.
2. Manipulative: (a) Injections of saline solution under the skin in the perineal region. (b) Distention of the bladder by hydrostatic pressure. (c) Tilting the foot of the bed so that the urine is thrown to the fundus of the bladder and the sensitive trigone is prevented from irritation.
3. Education: (a) Curtailing fluid intake. (b) Working at intervals. (c) Rewards and punishments.
4. Medical: Atropin and thyroid extract.
5. Suggestion: (a) Simple suggestion. (b) Hypnotic suggestion.

Cameron believes that the first four groups of therapeutic measures help only as a suggestion of cure.

To be successful, the treatment of enuresis must be conducted through and by means of the grown up persons who have the control of the children. To stop the development of enuresis in early infancy, we must intervene to prevent the concentration of the child's mind on the difficulty. The emphasis should be laid on successes, not failures. The child must be helped and encouraged to self-confidence and not rendered different or selfconscious. The child must learn to see that the thing is not so desperately tragic. He should be told that these persons always get well and that the trouble only goes on because he is worried about it and keeps thinking of it. If the whole environment of the child is bad which aggravates his nervous instability, he must be removed and put under the influence of someone else. In inveterate cases, hypnotic suggestion is always successful. Also, it is the home and the general management of the child which must be changed.

The house is the culture medium, and the crop grown in this case has not been satisfactory.

Pisek[10] believes that the great majority of cases of enuresis are due to a lack of control of the sphincter centers or the higher cerebral centers. If voluntary control is obtained over the lower centers, the patient is cured. Atropin may help a little, probably by decreasing the desire to urinate. Enuresis is more common in active, energetic children, who by night time give evidence of neuromuscular fatigue. The cure of these cases depends on detailed management, which includes rest, diet, bladder control exercises, psychic impressions and, in certain intractable cases, mechanical irritation of the sphincter. Having removed possible physical causes, such as phimosis or adenoids, the physician must acquaint himself with the details of the child's life, so that fatigue and excessive nerve stimulation may be avoided. Meats, meat soups, tea, coffee, pastry and all highly seasoned foods should be avoided. A two day rest cure is often beneficial, requiring that the child have his breakfast in bed, and he is not allowed out of bed until lunch time. Such a plan followed for two days each week, at the beginning and the end of the week often helps a great deal. The child should have a dry supper with as little liquid as possible after 4 p. m., and there should be no strenuous play in the afternoon. He is put to bed one hour after his supper and is taken up to urinate when the parents retire. During the day the child is required to urinate and to stop at the word of command. This teaches the higher centers to control the act. These control exercises are done at least three times a day in the presence of an attendant. The patient is given a report card which is filled out every morning indicating whether the bed was wet or dry and the number of times the control exercises were done. Young children who have not learned to write may affix a gold star for a dry bed and a red star for a wet one. These reports, which are mailed to the physician, make a deep impression and are extremely valuable adjuncts in the cure. (This is the most sensible article on enuresis that has been written this year.—L. W. H.)

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[10] Med. Clin. N. America **3**:350 (Sept.) 1919.

PYELITIS

Lozano and Ruiz[11] give full details of twenty-five cases, all but five in girls. The colon bacillus alone was found in 25 per cent., and associated with other germs in 33 per cent. The disease was primary in less than 15 per cent., measles in 25 per cent. and infectious sore throat in about 10 per cent. The absence of bacteria in the urine suggests possible tuberculosis, but they had one case with negative findings in which the pyelitis seemed of toxic and nontuberculous origin. There was no mortality in their twenty-five cases, except in three tuberculous children. They emphasize the necessity for surveillance of the kidneys during acute infectious disease, giving fluids in abundance. Small doses of hexamethylenamin may be useful. The genital organs should be kept scrupulously clean, and phimosis, etc., corrected.

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[11] Arch. espan. de Pediat. **3**:385 (July) 1919; abstr., J. A. M. A. **73**:1732 (Nov. 29) 1919.

Grulee[12] emphasizes the fact that cases of pyelitis rarely show any symptoms which point definitely to the involvement of the kidneys or the bladder. (Many cases present increased frequency, enuresis and dysuria, particularly if the bladder is involved.—L. W. H.) There are three types clinically, as follows:

1. The stormy type. The child is taken suddenly with high fever, convulsions and prostration or coma. In the first twenty-four hours the urine may contain no pus, but careful examination shows the presence of many motile bacilli in the sediment, and pus will be found usually at the end of forty-eight hours. These cases may run a rapidly fatal course, death occurring within two or three days. This is not a common type.

2. In this type, the baby becomes suddenly sick with a high fever, but there is usually slight prostration considering the height of the temperature, which may be 105 or 106 F. The prognosis is better than in the first type.

3. The third type is most frequent. Without the temperature being so alarming as in the first two types, it is still continuous. The child may be brought to the doctor on account of the temperature, or, perhaps, on account of loss of appetite or general debility. The course varies greatly. After the acute stage has passed, there is usually a low, irregular fever (if untreated) which may run for weeks. There is a marked liability to recurrence; one never knows when he has the disease under control.

Langer and Soldin[13] discuss the etiology of pyelitis. In most of the recorded investigations of the etiology of pyelitis which assert that the colon bacillus is the sole etiologic agent, the technic of investigation has not been without criticism. When it is realized in how many different diseases pyelitis may occur as a secondary complication, we begin to think that, perhaps, the primary offending bacterium has not been found because the colon bacillus may have overgrown it.

The authors believe that pyelitis is usually a secondary condition. It is especially likely to be secondary to "grippe," diphtheria, chickenpox, pemphigus, tuberculosis, furunculosis and epidemic meningitis; indeed, almost any acute infection in infancy is able to pave the way for a secondary pyelitis. A catheter specimen of adult urine is likely to be sterile. This is not true of infants. In a microscopic examination of the sediment, many bacteria can be seen, mostly gram-negative cocci, which belong to the group of *Streptococcus lacticus*. In children the *S. lacticus* has a tendency to implant itself in places of low resistance. It is doubtful if this organism is of much pathologic significance. The colon bacillus also may exist in normal urine, and normally there is an antagonism between the two organisms, the colon bacillus being kept down. In pyelitis the colon bacillus overgrows and probably gets into the kidneys through an injured intestinal mucosa.

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[12] Med. Clin. N. America **3**:93 (July) 1919.
[13] Ztschr. f. Kinderheilk. **5**:19 (July) 1919.

NEPHRITIS

Congenital Fetal Nephritis.—Dutrey and Widakovich[14] report the case of a prematurely born child of a woman who had 1.50 gm. per thousand albumin in the urine. Delivery was spontaneous, but the placenta weighed 1,950 gm., while the child weighed only 1,700 gm. There was general edema of the cord and membranes, and of the entire fetus. Lesions were found in the kidneys of the child, indicating chronic nephritis, and this nephritis in the child evidently had cooperated in the production of the edema. There was nothing to suggest syphilis in either mother or child. They know of only two other cases on record of congenital fetal nephritis, theirs being the third case to be published in accessible literature. In Sitzenffrei's case, the nephritis in the fetus was evidently acute.

Nephritis without Albuminuria.—Davidsohn describes three cases in which a focal glomerulonephritis was accompanied by many casts in the urine, but with slight and transient albuminuria or none at all. Oliguria was constant but not marked.

Purpuric Nephritis in Children.—Nobécourt's[15] patient was a girl, aged 17, who for four months had been presenting symptoms of rheumatoid purpura, but there had been no epistaxis, hematemesis or melena, and the purpuric eruption had never progressed to ecchymoses. Blood was noted in the urine on two occasions, and from 0.3 to 0.5 gm. albumin per liter was found constantly in the urine. These findings testify to simple albuminous nephritis persisting after the subsidence of the purpura. This purpuric nephritis is rarely accompanied by edema, uremia or high blood pressure. Even with retention of chlorids, this is slight and transient. On the other hand, purpuric nephritis without hematuria may be more tenacious; the albuminuria may persist for from two to four or even six months. Osler published the report of a case in which the purpura progressed in severe waves, with violent abdominal crises and edema. The urine contained albumin and casts but no blood, and the child finally died in uremic convulsions. In Nobécourt's own experience, bacteriologic examination was always negative. He never found azotemia, and the nephritis only exceptionally passed into a chronic phase. The hematuric form may subside completely in four or five weeks after an acute course, but usually it runs a subacute course and gradually improves, or it may persist indefinitely. The disease proved rapidly fatal, or only after several months, in about 25 per cent. of the cases cited. The characteristic features resemble those of cases of so-called primary nephritis or nephritis of unknown origin. Treatment should be addressed both to the purpura and to the nephritis. Nobécourt has been successful in some cases with subcutaneous injections of peptone. Calcium chlorid should also be tried. If it does no good, at least it does no harm. To act on the renal hemorrhage, tannin, ergot and krameria have been tried, but without much benefit. The main reliance is placed on dietetic measures, milk for a short time, then milk and vegetables, with a small amount of mutton or ham. Salt need not be discarded unless there is retention, but not much should be allowed as it may increase the hematuria. The child should be kept in bed a long time. Getting up may bring a wave of purpura and increase the albuminuria. Marini's patient eliminated 5.55 gm. of albumin in ten hours reclining, and 15.6 gm. when she got up. Careful treatment may ward off complications, but it does not modify the course materially.

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[14] Semana méd. **25**:661 (Dec. 5) 1919.

[15] Bull. méd. Par. **33**:503 (Sept. 13) 1919; abstr., J. A. M. A. **73**:1557 (Nov. 15) 1919.

Syphilitic Nephritis.—Hutinel[16] discusses nephritis occurring with congenital syphilis. He warns against the use of mercury in nephritis with congenital syphilis, as he has seen hematuria follow mercurial inunction. Intravenous injection of arsphenamin is the best procedure. Rapid improvement and definite cure must not be expected, as usually the nephritis is so far advanced that considerable scar tissue has probably formed. The nephritis may be of an acute nature, but does not tend to assume any special type. The kidney may develop symptoms after very slight causes, which indicates a lack of resisting power. The albuminuria is out of all proportion to the functional disturbance, and there is little tendency to edema.

Hemorrhagic Nephritis.—Buerger[17] believes that infection of the throat and tonsils is very important in this type of case. It is important to differentiate it from other genito-urinary conditions which give rise to hematuria. Very little is known of the pathology, but the pathologic changes may be very slight, and are likely to involve the glomeruli. It is usually difficult to find casts during the acute stage. Buerger calls special attention to the fact that there may be associated hemorrhage from the bladder, which gives rise to part of the hematuria.

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[16] Paris méd. **9**:65 (Jan. 25) 1919.

[17] Med. Rec. **94**:105 (Dec. 21) 1918.

Classification and Etiology.—Hill[18] in a general discussion of nephritis in childhood lays special stress on the superiority of a simple clinical classification over the old pathologic classification. It is often difficult or impossible to tell from the clinical condition of the patient what the microscopic appearance of the kidney in question is, and into what group of the pathologic classification the patient should be placed. Also in a large number of cases the kidney shows mixed types of injuries and cannot be put definitely into one group. The pathologist is studying the end results of morbid processes, while the clinician is more interested in the condition of the kidney at the time than in its appearance after death; also it is more vital to him to consider the kidney in its relation to the general condition of the patient than for him to be able to visualize its microscopic appearance. Moreover, a given kidney in the course of months or years may pass through several different classes of the pathologic grouping, according to how the damage is progressing.

Hill's classification is as follows: 1. Acute hemorrhagic nephritis. 2. Acute exudative nephritis. 3. Subacute nephritis. 4. Chronic nephritis (ordinary type). 5. Chronic nepritis with infantilism (very rare). He believes that infection is the most important etiologic factor, and that of all the infections, tonsillitis is the most important. Some other acute infections following which he has seen nephritis occur, are impetigo, scarlet fever, otitis media, pneumonia, purpura, alveolar abscess, cervical adenitis, and stomatitis.

The prognosis of acute nephritis in general he believes to be good, and also in chronic nephritis it is surprising to see how well many children do. The duration of acute nephritis in children is variable. The duration of forty-nine acute cases studied by him is shown. By duration is meant the time from the onset until the urine is albumin free, and shows no blood or casts in the sediment. Duration of acute nephritis: Two weeks, 1 case; three weeks, 4 cases; four weeks, 2 cases; five weeks, 3 cases; six weeks, 2 cases; seven weeks, 6 cases; eight weeks, 6 cases; nine weeks, 5 cases; twelve weeks or over, 12 cases.

Kidney Function.—Mosenthal[19] discusses the "Treatment of Retention of Waste Products in Nephritis." Some cases of chronic diffuse nephritis may have a persistent albuminuria for years without progressive encroachment on the kidney function. He cites the case of a woman, aged 40, who had had marked albuminuria for fourteen years, but had a phthalein excretion of 45 per cent. and a normal two hour test. Nocturnal polyuria is one of the first signs of an inefficient kidney. The reason of nocturnal polyuria in subacute or chronic nephritis is an inability of the kidney to eliminate sufficient solids during the daytime to make the night a period of comparative rest and inactivity. In order to determine the retention of waste products, studies of the blood are of value. Mosenthal gives the following figures for the normal nitrogenous nonprotein constituents per hundred c.c. of blood: Total nonprotein nitrogen, 30 mg.; urea nitrogen, 15 mg.; uric acid nitrogen, 2 mg.; creatinin nitrogen, 2 mg.

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[18] Am. J. Dis. Child. **17**:140 (April) 1919.

[19] Med. Clin. N. America **3**:353 (Sept.) 1919.

The first to increase in the blood is uric acid, next urea, and finally creatinin. The degree of increase of uric acid in the blood is probably the most delicate test of kidney function that there is, and it usually reveals an impairment of renal activity even before the two hour test does. The institution of a salt free diet is the best way to get rid of edema, and it almost always is effective. Hot packs and purging are useful adjuncts, but are not nearly so important as a salt free diet. It is well to avoid diuretics, and it is possible to make an oliguria worse by their use. There are two types of uremia. One is associated with marked retention of substance that should be eliminated by the kidney, the other occurs without any increase of urinary excretory products in the circulation, and while renal function is normal or nearly so. In uremia fluids should be forced, even if edema is present, and bleeding, followed by transfusion, may be of considerable value.

Functional Tests.—Scheel [20] discusses the significance of functional tests. Lack of urea retention is not always an assurance of good prognosis, as even with a low blood urea, uremia may develop. Scheel found the highest urea retention in cases of chronic glomerulonephritis and true contracted kidney. The retention of urea is independent of a tendency to edema. There is usually a high blood pressure with retention, but either may occur alone. The urea content of the blood is an excellent indication for the institution of a low protein diet.

MacLean and DeWesslow [21] regard as the most valuable tests for kidney function (1) the urea and nonprotein content of the blood; (2) the diastatic content of the urine; (3) the concentration of urea in the urine after the administration of urea by mouth, and (4) the chlorid content of the urine.

When the available renal tissue is just insufficient to maintain nitrogenous equilibrium with a normal blood urea concentration, the blood urea immediately increases in amount in proportion to the extent of the kidney lesion. When the damage to the kidney is insufficient to produce an increase in the blood urea, evidence of inadequate function can be obtained by other tests. In recent acute cases of nephritis there is generally some retention of urea, if the condition is at all severe. In unfavorable cases the concentration tends to increase, and in such patients the prognosis is often bad, in spite of a favorable clinical condition. In every case in which there was more than 300 mg. urea (not urea nitrogen [L. W. H.]) per hundred c.c. of blood, death occurred. A persistent increase in blood urea is a bad sign. Although there is a tendency to retention of urea in nearly all cases of acute nephritis, this is by no means true of chronic cases.

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[20] Norsk. Mag. f. Lægevidensk. **80**:363 (April) 1919; abstr., J. A. M. A. **72**:1800 (June 14) 1919.

[21] Quart. J. Med. **12**:347 (July) 1919.

The diastatic activity of the urine is important. The urine contains a ferment capable of hydrolyzing starch. The general opinion is that there is a marked decrease of diastase in the urine in nephritis, especially in the "chronic interstitial" type. The average amount of diastase in the urine of healthy individuals is remarkably constant, and the authors have found that it is usually considerably decreased in nephritis.

To determine the diastatic activity of the urine, three solutions are required. Their technic is as follows: (1) A 1 per cent. solution of soluble starch in distilled water; (2) a sodium chlorid solution of about 1 per cent. strength, and (3) a solution of iodin of about 0.5 per cent. strength. Ten tubes of equal size are used. Decreasing amounts of urine, from 0.6 to 0.06 c.c., are added. The total volume in each tube is then made up to 1 c.c. by the addition of the sodium chlorid solution, and finally 2 c.c. of the starch solution is added to each tube. The tubes are shaken and put into a water bath at 37 C. for thirty minutes. They are then removed and nearly filled with cold water to stop the ferment action. One drop of the iodin solution is added to each tube, and starting from number one note is taken of the first tube in which a blue tint is observed. This tube contains just that amount of urine which failed to convert all the starch into dextrin under the conditions of the test. The tube next to this, which may be clear or may show a reddish tint, is taken as the "limit," and from this tube the diastatic value of the urine is calculated. This so-called "d" value is empirically expressed in units, and represents the number of cubic centimeters of 0.1 per cent. starch solution which the particular urine is capable of digesting in one-half hour at 37 C. This value is obtained by dividing the number of cubic centimeters of starch solution used (2 c.c.) by the amount of urine required to digest this amount of starch. For instance, if the necessary quantity of urine was 0.1 c.c., then the diastatic value equals 20. In normals the "d" value varies from 6.6 to 30, the average being from 10 to 25. It varies to some extent at different times of the day, and on this account it is best, when possible, to test a sample from the twenty-four hour urine. Generally speaking, a constant value below 6.6 may be taken to indicate a defective kidney. As a rule, in the authors' experience, a patient with a very low diastatic value during the early acute period of the disease does not get on well.

If chlorid is specifically retained, this will lead to a retention of water in order to prevent excessive salt concentration in the body. It is one of the functions of the kidney to keep the concentration of the chlorids in the plasma in the vicinity of 0.6 per cent. In patients passing practically no salt in the blood, salt concentration is little, if any, higher than in a normal patient who may be passing 15 gm. of sodium chlorid in a day.

The authors say of the relation between anatomic and functional pathology: "It matters little whether a kidney is found to be large or small, white or red, rough or smooth, soft or hard. What is really of importance is to ascertain to what extent the kidney functions are interfered with during life, and it appears to us that little is to be gained by a more or less artificial grouping based chiefly upon the naked eye appearances of the organ after death."

As regards treatment, they advise a low protein diet in the early stages, but state that they are by no means certain that protein does harm during the subacute and convalescent stages. "We do not really know whether protein in ordinary amounts in the diet does harm in any case, but in the present state of our knowledge it seems important to enforce protein restriction in acute cases."

Williams and Humphreys [22] studied the blood sugar in fifty patients with nephritis. They found that it ranged from 0.06 to 0.25 per cent. In the early stages of acute nephritis the blood sugar is normal. In the last stages, when the patient is in uremia, the blood sugar is very high, often equal to that of severe cases of diabetes. Also, certain chronic cases characterized by high blood pressure show a high blood sugar. The blood sugar level is not appreciably influenced by carbohydrate restriction in the diet.

Failure in nitrogen metabolism precedes, often by months, the rise in blood sugar, so that the latter is of a rather serious prognostic significance.

Diet in Nephritis.—Lemierre [23] remarks that the discovery of the harmfulness of salt in certain forms of nephritis is one of the most important discoveries of recent years. Patients with extreme edema, such as used to be restricted to a milk diet over long periods, now are seen to improve and thrive under Widal and Javal's diet yielding 1,500 calories. It is made of 200 gm. bread made without salt; 200 gm. raw meat; 250 gm. potatoes; 50 gm. sugar and 30 centiliters each of wine and coffee. With dry uremia, in distinction to uremia with dropsy, Achard and Paisseau recommend a diet containing 50 gm. meat; 200 gm. potato; 100 gm. rice and 50 gm. butter, representing 1,030 calories. If there is no abnormal retention of salt, it is unnecessary to restrict the intake of salt. The intake of water should never be less than 1.5 liters as the kidney may not be able to eliminate urea unless it is well diluted; the polyuria, therefore, is necessary. In acute nephritis there is retention of all the elements of the urine, hence substances that produce these elements must not be taken, while water should be given freely to flush the kidneys.

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[22] Arch. Int. Med. **23**:537 (May) 1919.

[23] Paris Méd. **9**:34 (July 12) 1919; abstr., J. A. M. A. **73**:725 (Aug. 30) 1919.

Experimental Production of Nephritis.—Newburgh[24] studied the effect of high protein diets on the kidneys of rabbits. The tubular epithelium may suffer any degree of injury, including death, as a result of its efforts to remove certain abnormal substances from the blood. "May it not be true that the kidneys can secrete a certain amount of nitrogenous matter for an indefinite time without suffering harm, but that they will be injured if the quantity of some or all of the nitrogenous substances secreted be increased and kept at the higher level for some time?" In order to determine the truth of this supposition, Newburgh fed rabbits on diets abnormally high in protein, using egg-white, casein and soy beans. Renal injury was quickly and constantly produced in rabbits that ate several eggwhites daily. When the nitrogen metabolism was increased by means of casein, rabbits suffered no demonstrable renal injury from eating 15 gm. casein daily, but when the daily intake of casein was 30 gm., the nitrogen metabolism was about three times the normal, and a well marked deleterious effect on the kidney was noted. Rabbits that lived on soy beans for months regularly acquired chronic nephritis and frequently died of it. The nitrogen metabolism from this diet was about twice the normal.

99 Commonwealth Avenue.

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[24] Arch. Int. Med. **24**:359 (Oct.) 1919.

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American Journal of Diseases of Children

Vol. 20 OCTOBER, 1920 No. 4

ACROCEPHALY AND SCAPHOCEPHALY WITH SYMMETRICALLY DISTRIBUTED MALFORMATIONS OF THE EXTREMITIES *

A STUDY OF THE SO-CALLED "ACROCEPHALOSYNDACTYLISM" *

EDWARDS A. PARK, M.D., and GROVER F. POWERS, M.D.
BALTIMORE

That acrocephaly and syndactylism occur in combination has been generally appreciated since 1906, when the French pediatrician, Apert,[1] published the report of eight cases discovered in the literature and of one case from personal experience. Inasmuch as all the subjects exhibited deformities of the head, hands and feet so similar as to seem almost identical, Apert believed that the combination constituted a clinical entity. Accordingly, he gave to it the name "acrocephalosyndactylism." Since the publication of Apert's paper, other cases have been reported. We have been able to collect from the literature eleven cases exactly like those in Apert's series, and four others presenting the same deformity of the head but much less extensive deformities of the extremities. In addition, we have found four cases in which there was a characteristic affection of the head with slight malformations of the extremities, probably of the same nature as the malformations in the other cases but in the absence of exact description not proven. Including the cases of Apert's series and the patient who came under our own observation, made the subject of special report in this paper, the total number amounts to twenty-nine. Ten of the twenty-nine cases are reported from England, eight from France, four from Sweden, three from the United States, and one each from Italy, Germany, South America and Denmark. It is remarkable that only one case comes from German sources.

Moreover, we have been able to add to the above series two cases of scaphocephaly with malformations of the extremities, one case found reported in the literature and one from personal observation.

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* From the Department of Pediatrics, Johns Hopkins University.

[1] Apert, E.: De l'acrocéphalosyndactylie, Bull. et mém. Soc. méd. d. hôp. de Par. **23**: 1310, 1906.

Although the number of cases gathered together is small, we have gained the impression that the occurrence of the kind of defective development of the extremities in association with the kind of defective development of the head is not extremely uncommon. Dr. John Thomson of Edinburgh recently showed one of us photographs of two patients showing the combination of congenital defects, and the report of the existence of one in Boston and of another in New York has reached us while the present study was in progress.

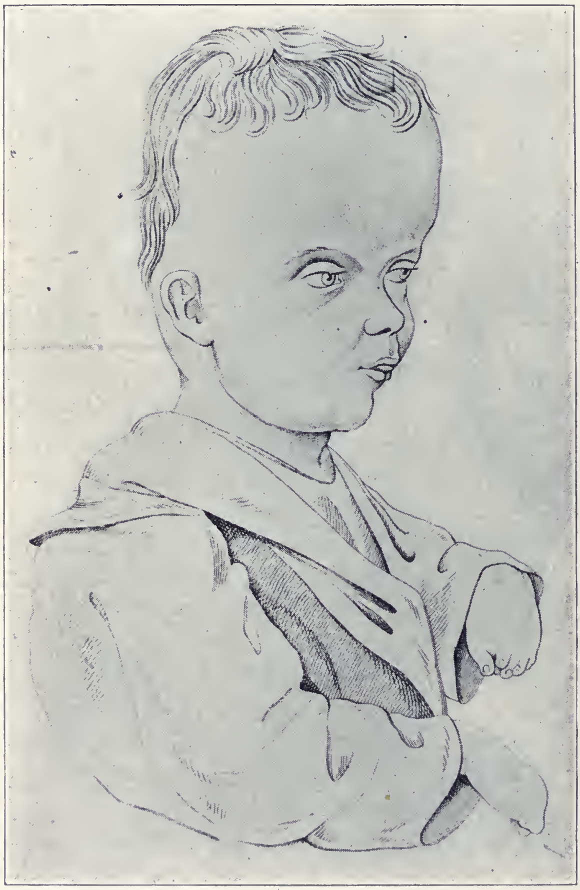

Fig. 1.—Photograph of an engraving from an anonymous atlas formerly belonging to the collection of Dr. Friedrich Ahlfeld, Leipzig, now No. 127287 of the Ahlfeld Teratological Collection, the gift of Francis M. Jencks, Johns Hopkins Medical School. It represents a child with acrobrachycephaly and symmetrical deformity of hands. (We are indebted to Dr. P. G. Shipley for the discovery of the engraving.)

REPORT OF CASE

D. H., aged 4 years and 8 months, of Jewish parentage, was born May 25, 1915.

Family History.—The father was aged 48 and the mother was aged 28 when the child was born. Both parents have always been well; they present no deformities. The patient is the eldest of three children; the younger two are normal. Parents know of no deformities in members of their respective families.[2]

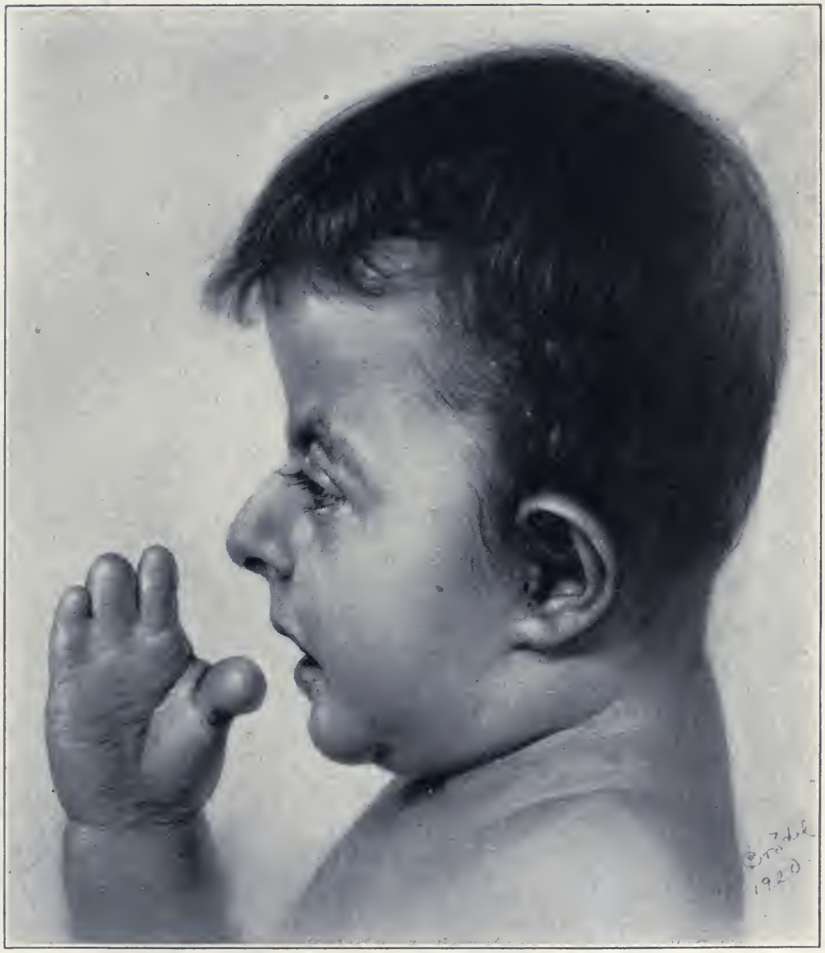

Fig. 2.—D. H. at age of 18 months.

Past History.—The child was born twenty-three days before term. The membranes ruptured six days before birth; the quantity of amniotic fluid discharged was said to have been large; labor began two days before birth.

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[2] The father has seen his grandparents and one great-grandparent and his five brothers and sisters. The mother has seen her parents, grandparents, and two greatgrandparents. Her seven brothers and sisters and five uncles and aunts were all normal.

Delivery with high forceps; child was cyanosed and not expected to live; scalp severely lacerated; deformities of head and extremities fully developed. The child was nursed for one year; has had no illnesses and has thrived. In April, 1916, at age of 11 months, a large mass of adenoids was removed; previously, there had been marked obstruction to breathing; otitis media followed the operation. On four occasions plastic operations were performed on the hands in an attempt to correct deformities.

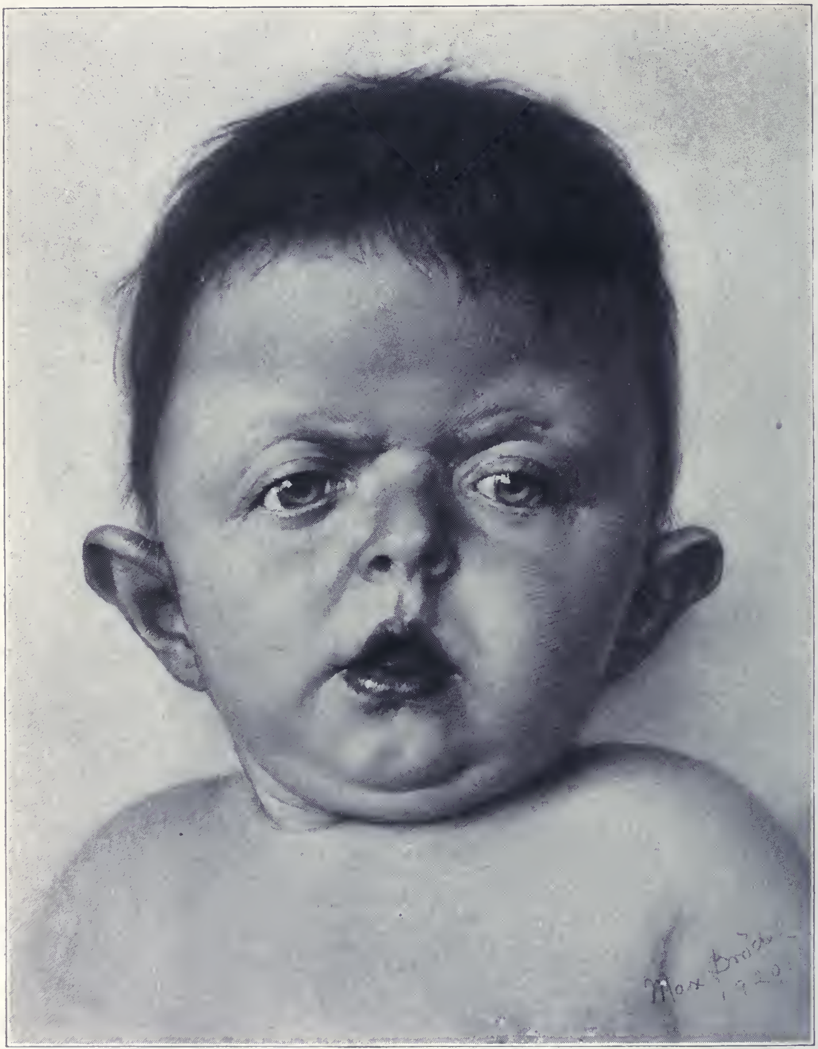

Fig. 3.—D. H. at age of 18 months.

Physical Examination at 18 Months of Age.—A well-nourished little girl; she holds up her head; sits unsupported; tries to stand when assisted; reaches for objects and pushes them away, but is unable to grasp them. She recognizes her father, and makes a sound interpreted by the parents as "daddy."

Her physical development may be judged from the following measurements: Weight, 9.5 kg. (average for her age, 10.6 kg.); height, 77 cm. (average, 75.6 cm.); circumference of chest, 47 cm. (average, 45.9 cm.); circumference of cranium, 44.5 cm. (average, 45.9 cm.).

The child presents no abnormalities except those of the head, hands and feet. Examination of urine and blood gives normal results. Von Pirquet test was negative; Wassermann reaction of blood was negative; cerebrospinal fluid was not obtained.

Head: The cranial vault is abnormally high; it is highest in the region of the posterior fontanel (Fig. 2). In contrast to the great height of the head is its extreme shortness and the marked breadth of face and forehead. The forehead rises almost sheer. Across it just above the superciliary ridges is a transverse groove. The portion of the forehead between this groove and the hair line bulges slightly forward. The back of the head is marked by neither curve nor prominence and is so flat that it appears to be in the same vertical plane as the neck. In cross section the cranium would approximate a square. The face is broadest in the region of the angular processes of the frontal bone and the zygomatic arches, which together form prominences causing the surface of the face to appear to be extended well beyond the eyes (Fig. 3). In consequence of the lateral prominences, the shape of the face is like that of a kite, the long diameter passing through the chin and nose. The face is unusually flat; the forehead, cheeks and chin appear to be almost in the same vertical plane. The head is symmetrical.

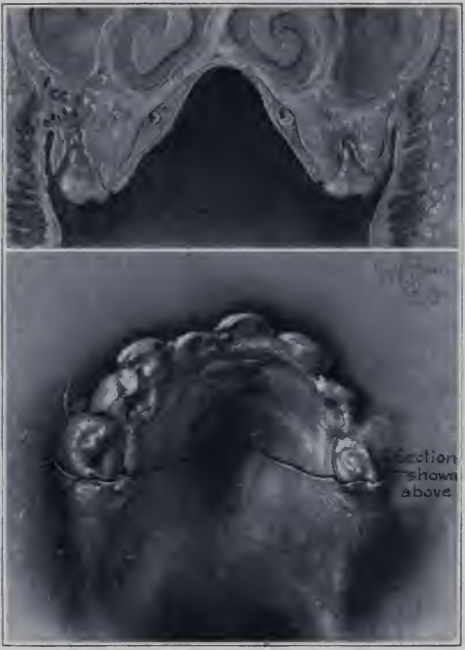

Fig. 4.—Roof of mouth of D. H. at age of 2½ years seen from below and in ideal cross-section.

Both fontanels are open; the anterior admits the tip of the index finger, and is placed farther forward than normal, bordering on the edge of the forehead. The large posterior fontanel is shaped like an isosceles triangle; from its apex the sagittal suture, just perceptible, may be palpated to its junction with the anterior fontanel; from its basal angles the lambdoidal sutures, also open, may be followed for a distance of 2 cm. When the patient was 10 months old the posterior fontanel was 7 cm. long and 4 cm. wide; a wormian bone was present, and the parietal margins were deeply serrated. At 18 months the posterior fontanel has decreased considerably in size; it now admits but the tips of two fingers. The coronal and temporoparietal sutures are closed. The site of the coronal suture is marked by a ridge. The metopic suture is open for a distance of about 3 cm. from the anterior fontanel.

Ears: The ears are large and flare outward in their upper and posterior parts. The point of junction of helix and scalp is on a lower horizontal plane than that passing through the external canthus. Hearing is acute; examination of the ear drums shows no abnormality.

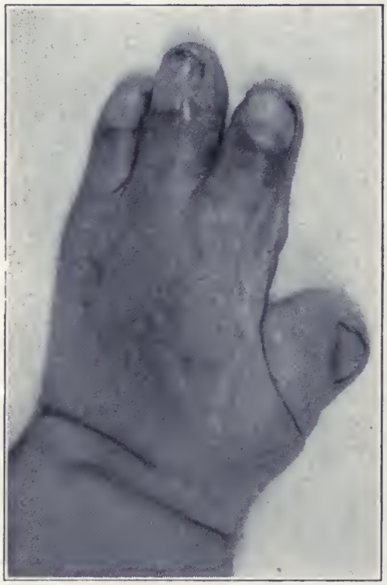

Fig. 5.—Left hand of D. H. after operation for correction of syndactyly. Age 18 months.

Eyes: The eyebrows are broad and flatly arched. The eyes, rather far apart, protrude slightly. The lids approximate perfectly. The eyeballs have the appearance of being slightly rotated in such manner that their transverse axes are directed outward and slightly downward. The palpebral apertures slant in an outward and downward direction; the external canthus is considerably lower than the internal. Vision seems unimpaired. The optic disks are normal. When the child was 6 months old, ophthalmoscopic examination showed the media to be clear and the papillae unusually distinct because of the encircling choroidal pigment. A grayish tint was imparted to the disks as the result of lack of pigment in the fundus. Not only was the pigment epithelial layer of the retina wanting, as in albinos, but the intercapillary islands of stromal pigment were missing as well. Thus, the vessels were clearly visible, and the underlying capillaries and venae vorticosae of the choroid were easily traced to the most minute ramifications.[3]

Nose: The nose is thin, rather short, almost straight, and sticks out from the line of the face in a more nearly horizontal direction than normal. The ridge of the nose emerges from the line of the forehead without preliminary depression, forming with the latter an angle estimated to be about 127 degrees. As seen from in front, the lower part of the nose is extremely narrow and has a pinched appearance. The nostrils are very thin, and the apertures abnormally small.[4] The nasal septum is almost straight anteriorly but posteriorly is deflected in such manner as to cause partial obstruction on both sides.

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[3] The reports of the ophthalmoscopic findings were made by Dr. L. B. Whitham.

Mouth: The mouth is small, and kept open. The upper lip is higher in its middle part than at its corners and projects forward; the open mouth forms an isosceles triangle of which the lower lip is the base. The chin is recessive. One tooth is present, a lower incisor. The hard palate is acutely arched and in cross section would appear as an inverted "V" (Fig. 4). The height of the arch measured from the level of the alveolar borders is 1.5 cm. There is malocclusion of the superior maxilla; the intermaxillary bone has not descended to the normal extent, so that the medial portion of the gums is on a higher level than the lateral. The uvula is normal.

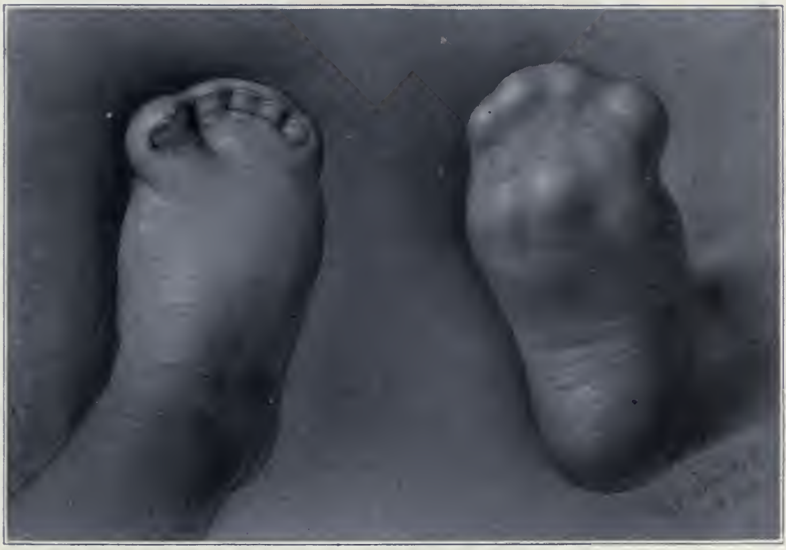

Fig. 6.—Right foot of D. H. at age of 18 months.

Hands: The hands are essentially alike in appearance. There is a pulpy mass of flesh without definite form, which corresponds to the body of the normal hand (Fig. 5). This mass is joined to the forearm almost directly with but little intervening wrist. To the outer side of the body of the hand at its middle is attached a lump of flesh with an osseous core which bears on its dorsal tip a small nail. This lump is the "thumb." The distal portion of the hand has a pinched appearance and is composed of three operatively created "fingers," projecting like the prongs of a trident. The artificially produced cleavage extends but a short distance above the terminal phalanges. There are two phalanges for each finger and a fairly well formed nail. Before operative interference the syndactylism was almost complete; the thumb and little finger elements were, however, partially demarcated from the rest. The nails of the fingers were fused. In the operations it was found that the phalanges of the outer two digits were synostosed, and in the right hand these were divided. The bandlike nail for the fingers, likewise, was divided into three portions, one for each finger.

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[4] The examination of nose and throat made by Dr. S. J. Crowe.

Feet: The feet are identical in appearance (Fig. 6). They suggest normal feet over which tightly fitting stockings of skin have been drawn, leaving the nails exposed; it is possible to distinguish on palpation a tarsus and metatarsus, and two phalanges for each toe. The feet appear much shorter than the normal for 18 months.

Roentgen-Ray Examination.—Head: Roentgenograms of the head (Fig. 7) show in a striking manner as in a silhouette the abnormal outline. More effectively than the photographs the roentgenogram demonstrates the high forehead, bulging in its superior portion, the high flat occiput, and the shortened fronto-occipital and increased vertical diameters. The fontanels are open and large. There is rarefaction of all the bones of the vault especially in the occipital region. In the frontal region digital impressions indicating convolutional atrophy are especially pronounced. The site of the coronal suture cannot be determined. The deeply serrated lambdoidal suture is seen. The middle and posterior cerebral fossae are deeper than normal. The posterior and superior orbital walls join at a slightly obtuse angle. The sphenoidal angle is probably increased. On the roentgenogram made when the patient

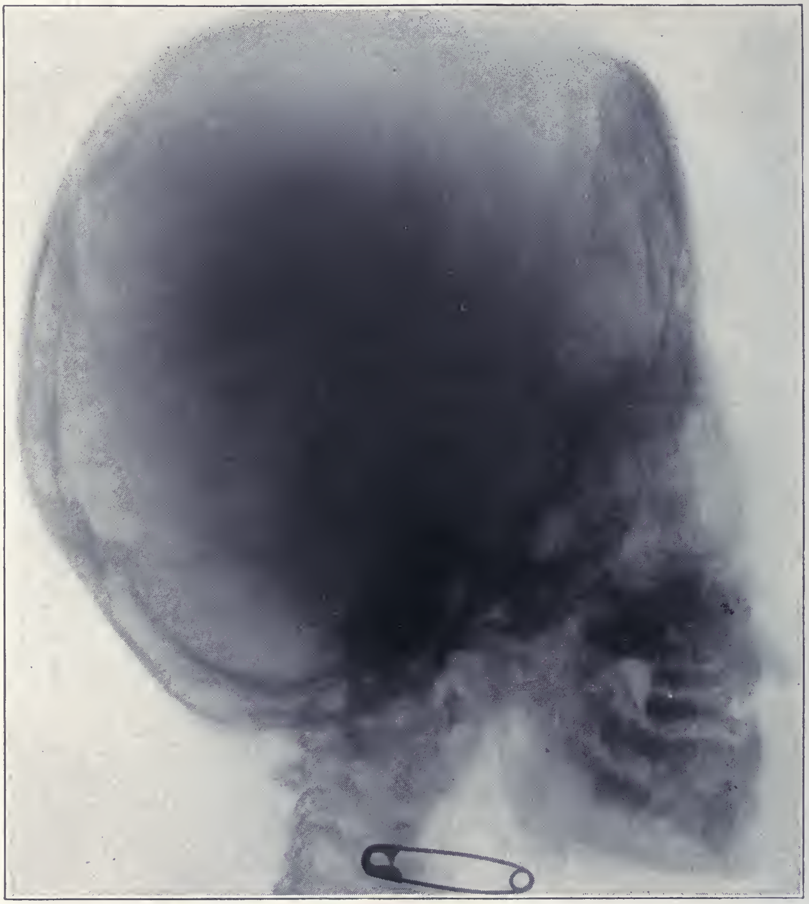

Fig. 7.—Roentgenogram of head of D. H., lateral view. Age 4 years 8 months.

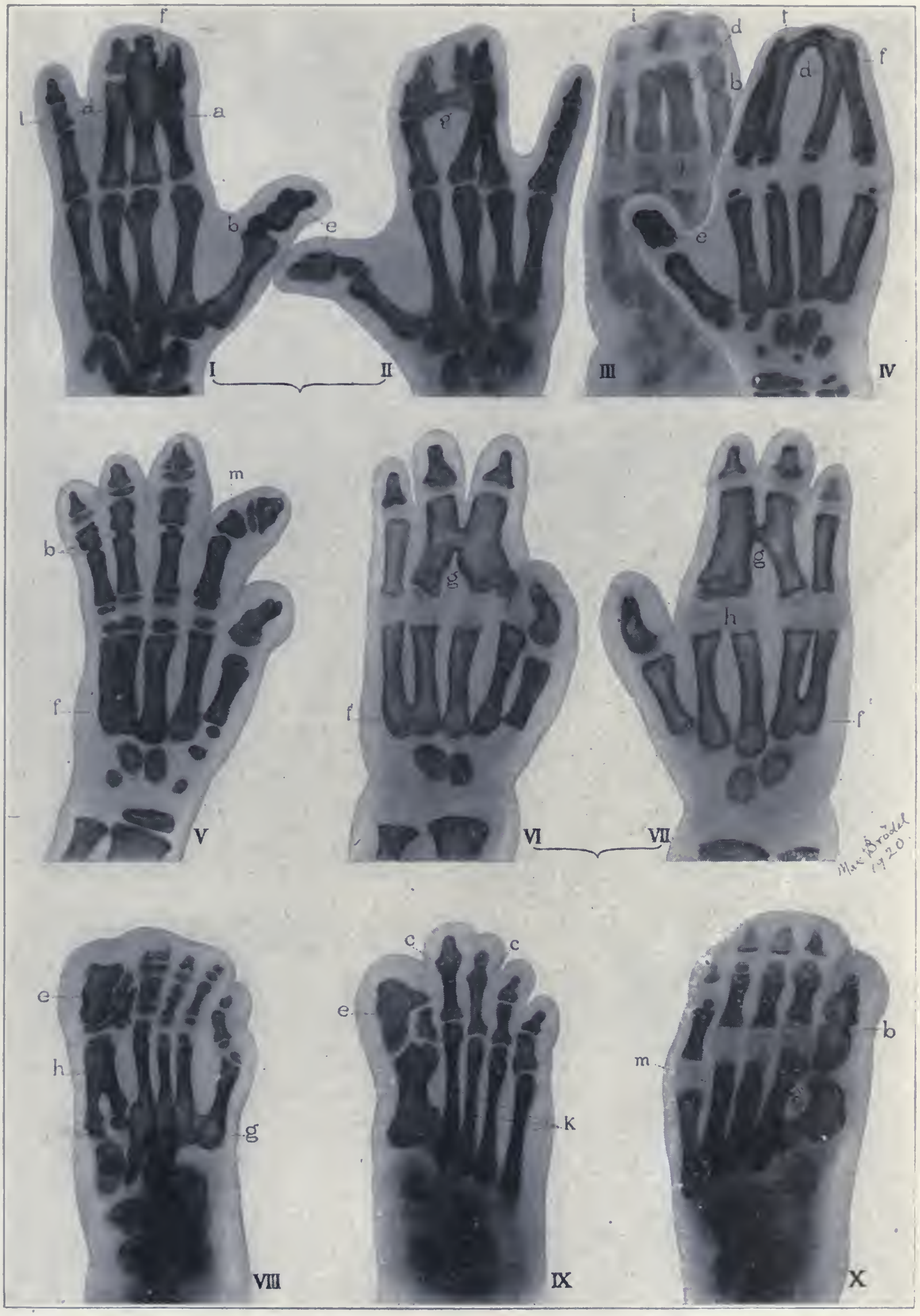

Fig. 8.—Drawings made from roentgenograms of hands and feet designed to illustrate types of malformations. Drawings I and II, Case 14, Gadelius; drawing III, Case 19, Ruh; drawing IV, Case 13, Davis; drawing V, Case 12, Bertolotti and Boidi Trotti; drawings VI and VII, authors' case; drawing VIII, Case 12, Bertolotti and Boidi Trotti; drawing IX, Case 14, Gadelius; drawing X, authors' case. For explanation of letters designating special types of deformity see text p. 264.

was 18 months old, the angle was estimated to be 160 degrees, whereas on the plate taken at 4 years 8 months of age it was considered to be 140 degrees.[5] The suture between the basi-occipital and basisphenoid bones was visible, indicating that synostosis had not taken place, and its distance from the basion was thought to be normal.

Extremities (Fig. 8, VI, VII and X, and Fig. 9).—Right Hand: There are only two ossification centers for the carpus, one for the os magnum, the other for the unciform. The five metacarpals are normal, except that the fifth and fourth seem to be united at their bases. The first and second phalanges of the ring finger are united and form a single, thick, irregularly shaped bone of about the length of the fourth metacarpal.[8] The first and second phalanges of the little finger are united and form a single bone almost as long as the metacarpal. There are three distal phalanges, one larger and longer than normal for the fused first and second phalanges of the index and middle fingers, one very large and broad distal phalanx for the ring finger, and a third, almost normal appearing phalanx, for the little finger. There is one irregular mass of bone which represents the two phalanges of the thumb. A rather broad interval exists between the distal ends of the metacarpal bones and the phalanges.

Left Hand: The bones of the left hand bear a remarkable similarity in respect to form and arrangement to those of the right. The large irregularly shaped bone representing the first and second phalanges of the index finger and middle finger, and the irregularly shaped bone representing the first and second phalanges of the ring finger, are, however, united in their middle portion.

Left Foot: The first metatarsal is abnormally large and greatly deformed. Its inner side is convex. From its outer side a bridge of bone a little less than 1 cm. in diameter runs transversely across the foot to unite with the second metatarsal. The second metatarsal approximates the normal in size and width, but is slightly bent at the point at which the bridge of bone from the first metatarsal joins it. The third metatarsal is normal, except for a distinct enlargement at the beginning of the lower third, which is not an exostosis but a general enlargement of the shaft. The fourth metatarsal presents a very slight enlargement in its lower third. The fifth metatarsal is normal. The first phalanx of the great toe is thick and irregularly shaped. The first phalanges of the other toes are probably fused with the second. The distal phalanx of the great toe is broad, pointed at the end and otherwise irregularly shaped. The terminal phalanges of the second, third, fourth and fifth toes are either normal or approximate the normal.

Right Foot: The right foot shows almost identical changes and is nearly the mirror image of the left. The bridge of bone extending from the first metatarsal to the second is not united with the latter, however, and the first and second phalanges of the big toe appear to be united.

There seems to be a general retardation in the growth of all the bones of the foot. There are no centers of ossification for the external and middle cuneiform and cuboid bones.

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[5] The sphenoidal angle is the obtuse angle formed at the anterior clinoid process by lines drawn from that point to the nasion and basion. An increase in this angle is referred to as a basilar lordosis and indicates a flattening of the base of the skull.[6] The normal angle has a value according to Welcker[7] of 134 degrees. The exact measurement of this angle during life is dependent on certain conditions: (1) A roentgenogram taken with parallel rays. (2) The sagittal plane of the head must be parallel to the plate (that this condition is not fulfilled, is demonstrated by the infrequency of superimposition of homologous structures). (3) On the roentgenogram one must be able to identify accurately the most anterior point of the foramen magnum, the basion.

[6] Schüller, A.: Roentgen diagnosis of diseases of the head. Authorized translation by Fred F. Stocking, with a foreword by Ernest Sachs, St. Louis. 1918, C. V. Mosby Co., p. 305.

[7] Welcker, H.: Untersuchungen über Wachstum und Bau des menschlichen Schädels, I. Theil, Leipzig, 1862.

[8] Prior to the operations done to correct the syndactyly this bone was united laterally to the bone representing the first and second phalanges of the index and middle fingers.

Physical Examination at 4 Years and 8 Months.—The child seems normal mentally. All the teeth are present but are crowded together. The fontanels are closed. The most striking feature is the marked bony ridge at the site of the coronal suture. The metopic suture is closed and its site is marked by a slight ridge. There is now an external squint of the right eye. Ophthalmoscopic examination revealed no fundus changes not mentioned in the previous report. Retinoscopy demonstrated a high degree of mixed astigmatism. Visual tests were quantitatively impracticable, but fair acuity of vision was present. It was impossible to demonstrate any appreciable deviation from the normal relationship between the fovea centralis and the optic disk, making it impossible to prove any external rotation of the eyeball on its anteroposterior axis.

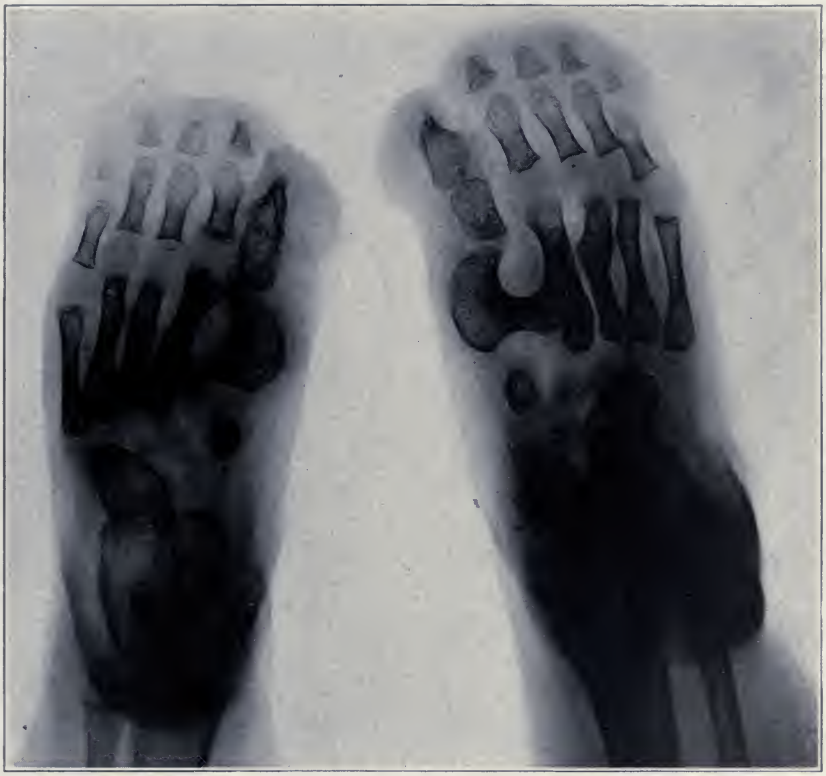

Fig. 9.—Roentgenogram of feet of D. H., age 18 months.

Roentgenograms made of the entire skeleton revealed no abnormalities excepting those of the head, hands and feet. Roentgenograms of the head showed the digital impressions to be more extensive and marked than at 18 months (Fig. 7).

Table 1, gives the measurements of our patient as compared with the average measurements of twenty normal children of a corresponding age.

TABLE 1.—Measurements in Our Case as Compared with Measurements in Twenty Normal Children

	D. H.* 18 Mos., Mm.	D. H.† 4½ Yrs., Mm.	Twenty Normal White Children, Average Age 4½ Years†		
			Average, Mm.	Maximum, Mm.	Minimum, Mm.
Greatest length of head	145	148	174.25	184	165
Greatest breadth of head	135	144	137.95	151	128
Projective ear height (tragus-vertex)	...	145	127.15	137	116
Nasion-Inion (base length)	120	139	152.95	172	138
Biauricular breadth (tragus-tragus)	110	114	113.9	123	105
Horizontal circumference of head	445	475	509.8	542	484
Sagittal arc (nasion-inion)	...	328	344.75	370	312
Transverse arc (tragus-tragus)	...	361	341.3	360	310
Smallest width of forehead	...	118	90.8	98	84
Bizygomatic breadth	120	132	112.05	121	103
Interocular breadth	30	34	27.75	32	21
External biorbital breadth	80	95	83.45	89	76
Length of ear (physiognomic)	...	57	52.70	58	47
Breadth of ear (physiognomic)	...	37	29.95	34	26
Average circumference (Horizontal Cir. + Sag. Arc + Nasion - Inion + Trans. Arc + Biauricular Breadth ÷ 3)	...	472.33	487.58	510	458.7
Cephalic index	103.8	97.3	79.18	25.1	73.9
$\frac{\text{Projected ear height} \times 100}{\text{Greatest length}}$	...	98	73	80.40	68
$\frac{\text{Ear length} \times \text{ear breadth} \times 100}{\text{Greatest length} \times \text{chin-vertex height}}$	...	7.23	4.78	5.72	3.69
Chin-vertex height	...	197			
Total face height	...	92			
Upper face height	...	55			
Nasal height	...	40			
Nasal breadth	...	24			
Breadth of mouth	...	33			
Acromion-radiale	...	179			
Radiale-stylion	...	128			
Length of hand	...	92			

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* Measurements by the authors.

† Measurements by Dr. A. H. Schultz, Research Associate, Department of Embryology, Carnegie Institute of Washington. Dr. Schultz made the following comments: The anterioposterior diameter of the head of D. H. is diminished (148 mm.; normal, 165-184 mm.; average 174 mm.) but the transverse diameter is slightly greater than the average but is within the range of normal variation (144 mm.; normal, 128-151 mm.; average, 137.95 mm.). The great difference between the cephalic index (see table) of D. H. and that of normal children is, therefore, largely due to the great reduction in the anterioposterior diameter rather than to the slight increase in the transversediameter. The cephalic index, 97.3, indicates hyperbrachycephaly and is never found in normal crania. The increase in the transverse diameter is most marked in the frontal region, the width of the forehead (188 mm.) being far outside the range of normal variation for this measurement (84-98 mm.; average, 90.8 mm.). Even the orbital region is modified by this increase in the frontal width; the external biorbital breadth in D. H. is 95 mm. whereas the average is only 83.45 mm.; the interorbital breadth is 34 mm., and in normal children 27.75 mm. Increase in the frontal breadth is also found in the zygomatic region of the face. The distance between the zygomatic arches in D. H. is 122 mm. whereas the normal values for this measurement range from 103 mm. to 121 mm. Other measurements of the face show nothing abnormal except insignificant differences in the dimensions of the nose (more prominent in D. H. than in the normal children) and the mouth (breadth of mouth 33 mm., normal 37 mm.). The chief compensation for the short anteroposterior diameter is found in the greatly increased height. The projective ear height of 145 mm. in D. H. is far outside the normal variation (116-137 mm.; average, 127.15 mm.); this measurement in D. H. is 98 per cent. of the anteroposterior diameter, whereas its average value for the normal children was only 73 per cent. of the average anteroposterior diameter. The base of the skull shows great reduction in length; the nasion to inion measurement is 139 mm. in D. H.. whereas it averages 152.95 mm. in normal children. On the other hand, the breadth of the base of the skull appears to be normal. (Biauricular breadth in D. H. is 114 mm.; average in normal children, 113.9 mm.) The capacity of the cranium is indicated by the average of the circumferences in the three dimensions. This is determined according to the formula: Horizontal circumference + sagittal arc + nasion-inion length + transverse arc + biauricular breadth ÷ 3. The value of this average circumference in D. H. is 472.33, whereas its average value in normal children is 487.63. Thus the cranial capacity is somewhat reduced. This would suggest that the retarded growth in length was not quite compensated for by the increase in breadth and height. The index for the relative size of the ear as determined from the formula: Ear length × ear breadth × 100 ÷ chin-vertex height × greatest length is 7.23 in D. H. but only 4.78 in normal children; this indicates an abnormally large ear.

ANALYSIS OF THE DEFORMITIES IN THE FIRST TWENTY-FIVE CASES OF ACROBRACHYCEPHALY [9]

Gadelius [10] makes the remark, "One is tempted to say of this group of patients [showing acrocephaly with symmetrical syndactylism] as of Mongolian idiots that the characteristics which mark the individual are lacking, since one abnormal person belonging to the group resembles the other." "Man vore här liksom vid mongolismen frestad att säga, at individuella särdrag saknas, det varje undermalig individ tillhörande denna form är lik den andre,"[10] page 21. As a matter of fact the finer facial characteristics and traits of expression are lost sight of in the presence of the gross defects of head and extremities so uniform and conspicuous as to confer a sort of species resemblance.

Although the descriptions in the twenty-five cases assembled suffice to establish the diagnosis, yet in a number of instances they are too incomplete and indefinite to permit of analytic study. The deficiencies in the written records are, in large part, compensated for by photographs and roentgenograms. From the combined sources of information it is possible to make the following generalizations in regard to the deformities of the head in the series of cases in question:

The head is abnormally high, short and broad. The occiput is almost flat. The eyeballs protrude and have the appearance of being obliquely set in such manner that their transverse axes are inclined outward and slightly downward. The palpebral aperture invariably has an oblique direction, so that the external canthus lies at a considerably lower level than the internal canthus.

A mere glance at the photograph of any case is sufficient to show that the vertical diameter of the head is greatly increased and that the increased height is due to an abnormal extension upwards of the cranial vault. The highest point of the head is subject to considerable variation. In the cases of Magnan and Galippe [11] (Case 3), Apert [1] (Case 10). Bertolotti and Boidi Trotti [12 b,c.] (Case 12) and Dodd and McMullen [13] (Case 21), it is stated to have been in the region of the anterior fontanel; in the case described by Davis[14] (Case 13), however, in our own case, and a number of other cases, as judged by photographs, it was in the region of the posterior fontanel. In the case of Rieping[15] (Case 20), the highest point lay between the fontanels immediately above the external auditory meatus. In none of the cases, except that of Rieping, so far as it is possible to judge from photographs, was the highest point of the head so much higher than the rest as to justify the term "oxycephaly," and in no case, unless possibly that of Ruh,[16] could the head be described as "tower" shaped.

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[9] The abstracts of the twenty-four cases additional to our own will be found at the conclusion of the article.

[10] Gadelius, B.: En sällsynt form af idioti med karakteristiska utvecklingsanomalier. Akrocephalosyndaktyli (Apert), Nord. med. Ark. **15:** Pt. 2, 1, 1915.

[11] Magnan, and Galippe, V.: Accumulation de stigmates physiques chéz un débile: brachycéphalie, plagiocéphalie, acrocéphalie, asymétrie faciale, atrésie buccale, syndactylie des quatre extrémités, Compt. rend. Soc. de biol. **4:** Pt. 2, 277, 1892.

[12] Bertolotti, M.: (a) Le syndrome oxycéphalique ou syndrome de craniosynostose pathologique, Presse méd. **22:** 332, 1914. Bertolotti, M., and Boidi Trotti, G.: (b) L'acrocefalosindattilia di Apert considerata come una varieta fetale della cranio-sinostosi patologica, Riforma med. **31:** 679, 1915. Boidi-Trotti G.: (c) Un caso di acrocefalosindattilia, Gior. d. r. Accad. di med. di Torino **21:** 123, 1915.

[13] Dodd, H. W., and McMullen, W. H.: A case of congenital deformity of the skull associated with ocular defects, Lancet **1:** 1665, 1903.

The height of the head has not excited more comment than its shortness. As a glance at the photographs of our patient (Figs. 2 and 3) will show, the shortness of the anteroposterior diameter of the head is due chiefly to the great reduction in the prominence of the occiput. In a number of the cases the back of the head was described as flush with the neck. It is a striking fact that the surfaces of the face and back of the head are almost parallel. In Rieping's case alone (Case 20) does the occipital prominence appear to have been preserved. In Wheaton's two subjects[17] (Cases 4 and 5), aged 2 and 3 months, respectively, the length of the head was only 8.6 cm.; in Ruh's patient[16] (Case 19), aged 6 months, 11 cm.; in Bertolotti and Boidi Trotti's patient[12] (Case 12), aged 5 years, only 13 cm.; and in the first of Gadelius' series of four patients[10] (Case 14), a man aged 24 years, but 16.5 cm. In several cases the statement is made that the occipital protuberance was absent, but in one that it was unusually large.

The head relatively and actually is broad. There exists a true brachycephaly. In the ten cases in which the cranial index was recorded it ranged from 87 (Case 20, Rieping) as a minimum to 115 (Case 12, Bertolotti and Boidi Trotti) as a maximum, and in five it was 100 or more. In Ruh's and Rieping's cases the greatest transverse diameter was in the temporal region (bitemporal diameter 11.5 cm., biparietal diameter 10.5 cm. [Ruh]; bitemporal 9.5 cm., biparietal 6 cm. [Rieping]); in the other cases in which any statement was made, in the parietal region.

From the description and photographs it appears that in only one case was there asymmetry of the head. Magnan and Galippe state that in their subject (Case 3) the right frontal and the left mastoid regions were prominent, whereas the left frontal and right mastoid regions were flattened. The right side of the forehead was higher than the left. Evidently this case was an instance of plagiocephaly as well as of acrobrachycephaly.

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[14] Davis, B. F.: Acrocephalosyndactylism, Am. J. Dis. Child. **9**: 446 (March) 1915; also, J. Nerv. & Ment. Dis. **42**: 567. 1915.

[15] Rieping, A.: Zur Pathogenese des Turmschädels, Deutsch. Ztschr. f. Chir. **148**: 1, 1919.

[16] Ruh, H. O.: Acrocephalosyndactylism, a teratological type, Am. J. Dis. Child. **11**: 281 (Feb.) 1916.

[17] Wheaton, S. W.: Two specimens of congenital cranial deformity in infants associated with fusion of the fingers and toes, Tr. Path. Soc., London **45**: 238, 1894.

The circumference of the head was slightly below the normal in the cases in which record was made. Table 2 demonstrates this fact.

The face in our case was kite-shaped, as already pointed out, due to the prominence of the skull in the region of the angular processes of the frontal bone and the zygomatic arches. Davis describes the face in his case as diamond shaped, and photographs which accompany the case reports of other writers would indicate that the face was particularly wide at or above the level of the zygomatic arches.

TABLE 2.—Circumference of Head in Our Series of Cases as Compared to Average for Age

Case No.	Author	Age	Circumference Cm.	Average for Age* Cm.
12	Bertolotti and Boidi Trotti..	5 years	49	51
13	Davis........................	3½ years	48	48.5
14	Gadelius......................	24 years	54	55 (at 15 yrs.)
15	Gadelius......................	6 years	47	51 (at 5 yrs.)
19	Ruh...........................	6 months	38	43
18	DeSalterain...................	8 years	51	52 (at 5 yrs.)
7	Ireland.......................	Adult	55	55 (at 15 yrs.)
21	Dodd and McMullen	7 years	48.5	52
22	Hutchinson....................	1 year	41.8	44.7
20	Rieping.......................	New born	31	35.5
	Park and Powers.............	18 months	44.5	45.9

* Data from Holt and Howland.[18]

Mention has already been made of the abnormal height and breadth of the forehead. We need add merely that in a number of the cases a horizontal groove passed across the forehead just above the superciliary ridges, and above the groove the forehead bulged forward. Indeed, a prominence of the upper part of the forehead is probably a very common feature of the deformity of the head. Specific mention of its existence was made in ten cases. In the cases in which the metopic suture had already closed, the prominence was composed of bone, but in those cases in which it was patent the prominence was due to the protrusion of the soft parts. In the case described by Maygrier [19] and Fournier [20] the prominence of the mid-portion of the forehead was thought to be a meningocele. The metopic suture was 2 cm. wide, and the adjacent margins of the frontal bone bent forward. Probably, in the majority of cases in which closure of the sutures had taken place, the bony prominence in the middle of the forehead signified that the metopic suture had been patent, and that ossification had roofed over the protruding soft tissues. In the patient of Camus,[21] for example, aged 10½ years, the bony prominence was described as "keel shaped," and as being especially marked in its lower part. It occupied the median line of the forehead, and evidently corresponded in its position to the metopic suture. In some cases, however, the bony ridge in the situation of the metopic suture may have signified premature closure of the suture (Case 19, Ruh). The superciliary ridges have been variously described as "prominent" or "flat."

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[18] Holt, L. E., and Howland, J.: The Diseases of Infancy and Childhood, 7th Edition, New York and London, 1916, D. Appleton Co., p. 1180.

[19] Maygrier: Présentation d'un enfant atteint de malformations du crâne (porencéphalie) et des extrémités (syndactylie) par hiérédo-syphilis, Bull. Soc. d'obst. de Par. 28, 1898.

[20] Fournier, E.: Stigmates dystrophiques de l'hérédo-syphilis. Paris, 1898, Reuff et Cie, p. 372. [Obs. 328, p. 244.]

A subject of great importance in its bearing on the question of the part of the skull primarily affected is the condition of the fontanels and sutures (Table 3). Of the twenty-five subjects of the deformity, eleven were less than 18 months old. Of these six were new-born infants; the remaining five were aged 2, 5, 6, 10[22] and 12 months, respectively. In the case of the patients of Troquart[23] (Case 1) and Dubrisay[24] (Case 8), both new-born children, and very incompletely described, mention is made only in regard to the metopic suture. In Dubrisay's patient the metopic suture was no less than 2 cm. wide and in Troquart's it was patent almost to the root of the nose. It may be assumed in both instances that the anterior fontanel was open. In the case of the new-born child described by Magrier and Fournier, the anterior fontanel was 4 cm. wide, the posterior fontanel "extremely" wide. The sagittal suture became so broad between the fontanels that it formed an "accessory fontanel," shaped like a lozenge; the metopic suture was 2 cm. wide and extended from the root of the nose to the anterior fontanel. In the case of the two babies described by Wheaton, aged 2 and 3 months, respectively, a "continuous suture" ran from the posterior fontanel to the root of the nose. The metopic suture was 1¼ inches wide. The posterior fontanel must have been extremely large, for a wormian bone was present. In one of the two cases a wormian bone lay in the metopic suture also. The margins of the bones bounding fontanels and sutures were extremely irregular. In the new-born child described by Rieping the anterior fontanel was open but small, the posterior fontanel extremely large and shaped like an isoceles triangle. The base of the triangle measured 40 mm., the perpendicular 50 mm. The metopic suture was sufficiently large to contain a wormian bone 6 mm. broad and 44 mm. long. The sagittal suture was apparently partially closed and formed a ridge. The coronal suture was partially synostosed. The sphenofrontal suture apparently was closed. In our patient, at 10 months of age, when the first examination of the skull was made, the posterior fontanel was 7 cm. long, 4 cm. wide and contained a wormian bone. The margins of the parietal bone bordering the fontanel were deeply serrated. Even at the eighteenth month the posterior fontanel was open, and admitted the tips of two fingers. The anterior fontanel, also, was open, admitting the tip of one finger; the lambdoidal suture, still patent, could be followed for a distance of 2 cm. The metopic suture was open for a distance of 3 cm. The coronal suture was closed and probably synostosed. Its course was indicated by a well defined ridge. In the very incompletely described patient of Apert, aged 5 months, no mention of fontanels or sutures is made. It is evident, however, from the context that the anterior fontanel at least was open.[25]

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[21] Camus, M.: Accumulation de stigmates physiques chez un dégénéré, Compt. rend. Soc. de biol. **55**:1555, 1903.

[22] Our own case is included here because an examination of the patient was made at the age of 10 mos. as well as later.

[23] Troquart, R.: Syndactylie et malformations diverses, Mém. et bull. Soc. de méd. et chir. de Bordeaux, 69, 1886.

[24] Dubrisay, L.: Enfant atteint de porencéphalie et de syndactylie, issu d'une mere syphilitique, Bull. Soc. d'obst. de Par., 81, 1898.

TABLE 3.—CONDITION OF FONTANELS AND SUTURES IN SUBJECTS OF ACROBRACHYCEPHALY UNDER 18 MONTHS OF AGE *

Case No.	Author	Anterior Fontanel	Posterior Fontanel	Sagittal	Metopic	Coronal	Lambdoidal
1	Troquart............	Open†	Not stated	Not stated	Open	Not stated	Not stated
4	Wheaton 1..........	Open	Open	Open	Open	Not stated	Not stated
5	Wheaton 2..........	Open	Open	Open	Open	Not stated	Not stated
6	Maygrier; Fournier.	Open	Open	Open	Open	Not stated	Not stated
8	Dubrisay............	Open†	Not stated	Not stated	Open	Not stated	Not stated
10	Apert................	Open	Not stated	Probably open	Probably open	Probably open	Not stated
19	Ruh..................	Open	Open	Open	Closed	Open	Open
22	Hutchinson..........	Open	Not stated	"Closed"	Open	"Closed"	Not stated
24	Cameron............	Open†	Not stated	Not stated	Not stated	Not stated	Not stated
20	Rieping..............	Open	Open	Closed (?)	Open	Closed	Not stated
	Park and Powers....	Open	Open	Open	Open	Closed	Open

* It must be borne in mind that with the exception of the cases of Rieping and Wheaton all the data were obtained from clinical examination and in the majority of the cases were grossly incomplete.

† Condition of anterior fontanel not described. We assume, however, that, had there been so striking a departure from the normal as a closed anterior fontanel at birth, a statement to that effect would have been made.

Thus, we see that in all the subjects of the malformations less than 18 months of age at the time of examination, parts of the cranial vault were membranous, in the majority of instances to a very much greater extent than normal, and in eight cases, at least, the metopic suture was open. In Davis' patient (Case 13) the metopic suture was open at 3½ years. Only in the patient of Ruh was the metopic suture closed.

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[25] Apert states that "the anterior fontanel occupied the summit of the head[1] p. 1313.

In the photographs which accompany the case reports the eyes appear to be far apart. In regard to every subject of the malformations, with the exception of the three infants described by Wheaton and Rieping, seen only after death, it is specifically stated that the eyeballs were protuberant. In the patient of Magnan and Galippe, the eyeballs protruded to such an extent that they appeared to be pedunculated and extended 1 cm. in front of the plane of the forehead. In the patient of Donaldson[26] (Case 25), the protrusion of the eyeballs was so extreme that the right eyeball had become dislocated on eleven different occasions, so that manual replacement became necessary.

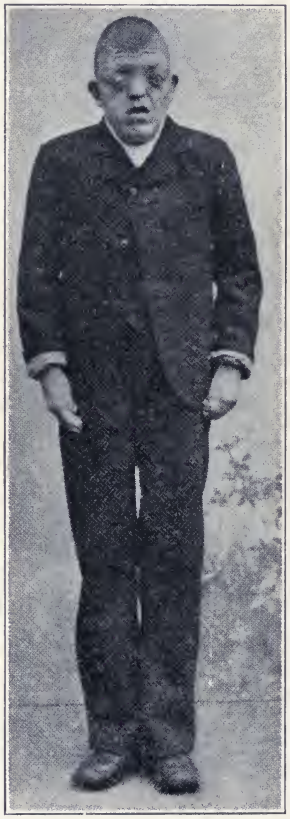

Fig. 10.—The patient of Ireland. Although Ireland makes no statement in regard to the elbows, the photograph suggests that the elbows were malformed in such manner that they could not be completely extended. The hands reach scarcely below the level of the pelvis and the arms are held in a partially flexed condition. Reproduced from Gadelius. (Case 7, our series.)

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[26] Donaldson, E.: A Case of Deformity of the Head and Dysostosis, Tr. Ophth. Soc. U. Kingdom, Lond. **23**: 264, 1903.

In most of the more carefully described cases the statement is made that the eyeballs were set obliquely in such manner that their horizontal axes passed from within slightly downward. As already pointed out, however, in the description of our own case, it is very difficult to be certain that the eyeballs themselves were actually rotated. There is no doubt, however, that in every member of the series of whom there is photographic record, the palpebral aperture slanted outward and downward. In Ireland's patient[27] (Case 7, Fig. 10), the eyeballs were described as having divergent axes; in the first case of Gadelius' series (Case 14, Fig. 11), the right eye failed to coordinate with the left, and in his third case (Case 16, Fig 12) there was external strabismus. In our case also external squint was present.

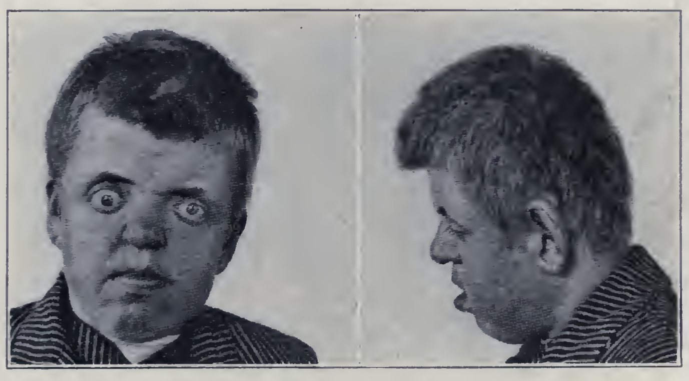

Fig. 11.—A patient of Gadelius. The acrocephaly and brachycephaly, prominence of the eyeballs, slant of the palpebral apertures, are well shown (Case 14, reproduced from Gadelius).

The eye grounds have been examined in comparatively few cases; in our own and in Cameron's patient[28] (Case 24) they were normal. In Bertolotti and Boidi Trotti's patient optic neuritis existed; in Davis' patient the nerve head was reported as gray, the margins blurred, and some swelling present; in deSalterain's patient[29] (Fig. 13) staphyloma was present on the right side making examination of the disk impossible; on the left side the disk showed enlargement in the transverse diameter. Diminution in the acuity of vision was noted only in the patient of Bertolotti and Boidi Trotti.

The nose has been variously described as "large and thick," "flat and depressed," "the root depressed or flattened," "short and broad,"

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[27] Ireland, W. W.: The mental affections of children, idiocy, imbecility and insanity, London. 1898, J. A. Churchill, p. 448.

[28] Cameron, H. C.: Case of achondroplasia with hydrocephalus, Proc. Roy. Soc. Med., London **12,** Sect. Dis. Child., 8, 1919.

[29] deSalterain, J.: (a) A proposito de un caso de oxicefalia (Comunicacion a la Sociedad de Pediatria de Montevideo; Sesión del 15 Junio de 1917). Arch. Latinó-am. de pediat., Buenos Aires, No. 4, 1917. (b) A proposito de un caso de oxicefalia (A propos d'un cas d'oxycephalie) Sociedad de Pediatria de Montevideo, 15 juin, 1917, Rev. med. d. Uruguay **20:** 398, 1917.

"shapeless," "small and thin." In three cases it deviated to the left. From examination of photographs we should make the observation that the nose, no matter what were its lateral dimensions, was not long, and that it pointed in a more nearly horizontal direction than usual. The curious projection of the nose from the face is well illustrated in our patient (Fig. 2). The nasal apertures in our patient and in the one of Bertolotti and Boidi Trotti were extremely small. Nasal obstruction has been observed in several of the cases, and was probably present in all, due to malformations of the nasal passages, or the nasopharynx, to adenoids, or to all three.

The facies is that of chronic nasal obstruction. As shown so well in the photographs (Figs. 10, 11, 12, 13 and 14), the mouth is open; the middle portion of the upper lip is elevated, and occupies a more forward position than normal. The lower lip is flat. The mouth as a whole, therefore, forms an isoceles triangle with the apex upward.

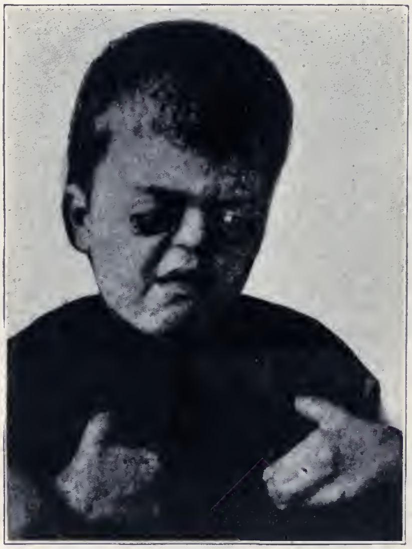

Fig. 12.—A patient of Gadelius. The height of the head, prominence of the eyeballs, the external strabismus, the slant of the palpebral apertures and syndactylous malformations of the hands are well shown (Case 16). Reproduced from Gadelius.

The hard palate was extremely narrow and high in all cases in which mention was made with the exception of the patient of Dubrisay and probably constitutes a constant feature of the malformation of the head (Fig. 4). In Davis' patient the palate was not only narrow and sharply arched but there was a shelflike projection along the alveolar margins. In Camus' patient the alveolar margins joined in such a way as to produce a recess in the upper part of the mouth immediately above and behind the incisor teeth. In at least five of the cases the hard palate was cleft. It is interesting and important to note that in no instance was the cleft in the palate complete or accompanied by harelip. In the third of Gadelius' series (Case 16) the cleft in the hard palate was anterior, lying between the incisor teeth.[30] In the other cases we infer that the cleft was in the central or posterior portions. In six other cases the soft palate or uvula was bifid, and in one case, that of Régis,[31] the soft palate was said to be lacking. In twelve cases out of twenty-one, therefore, abnormalities in the formation of the hard or soft palate were noted.

Troquart stated that in his 18 months old patient dentition was normal, and Gadelius found the teeth in the first member of his series (Case 14) in their normal situations. Certainly, in the majority of subjects beyond the age of infancy dentition was abnormal. In Bertolotti and Boidi Trotti's patient some of the incisors were behind the others.

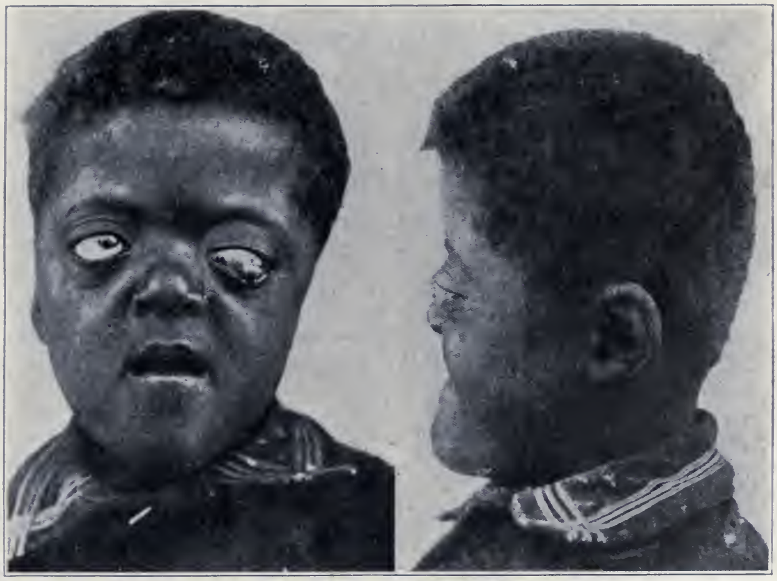

Fig. 13.—Photographs of child with acrobrachycephaly, reproduced from De Salterain. Age 8 years.

The lower jaw presents no distinctive abnormality. In three cases it was said to be prognathic, and in two recessive.

The main features of the deformities of hands and feet can be summarized in a few words.[32] In one group the syndactylism of the hands was complete. The fused fingers, thumb, and body of the hand formed a mass shaped like the bowl of a spoon, the concavity of the spoon corresponding to the palmar surface. The deformity in this group can be simulated by thrusting the hand into the toe of a tight stocking that crowds the ends of the fingers together. In another group all the fingers were completely syndactylous; the thumbs, however, though misshapen and functionally abnormal, were free (Fig. 12). The shape of the hand in this group resembled that of the normal hand in a tight fitting mitten. In a third group the thumbs were free and the little fingers partially free (Fig. 15). In a fourth group the little fingers were free for a part of their extent. The thumbs, however, were completely joined to the other fingers.

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[30] An undescended intermaxillary bone.

[31] Régis, E.: Precis de psychiatrie. Ed. 5, Paris, 1914, O. Doin et fils, p. 1230.

[32] For the exact details in regard to the deformities of hands and feet and the bizarre form and arrangement of the finger and toe nails the reader is referred to the abstracts of the case reports.

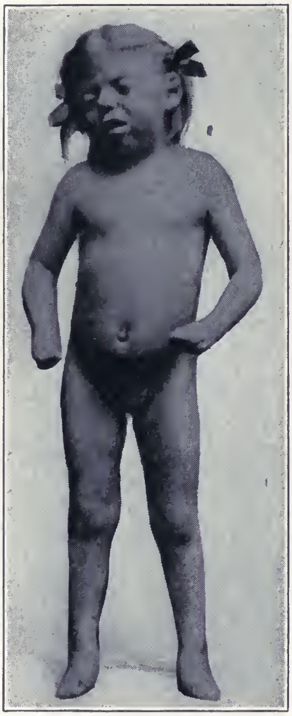

Fig. 14.—A patient of Gadelius. The photograph reproduced from Gradelius shows the prominence of the eyes, the slant of the palpebral apertures, the open mouth and syndactylism of hands and feet (Case 15).

As regards the feet in the four groups of cases mentioned, either a condition of complete syndactylism existed (Fig. 6) or the great toes alone were free. Hallux varus was invariably present in all cases in which record was made (Fig. 16).

In the cases not falling into the four groups mentioned (Cases 21, 22, 23 and 24) the deformities of the hands and feet were slight but definite.

CASE 21: The phalanges of the great toes were abnormally broad; hallux varus; interphalangeal joints ankylosed.

CASE 22: Middle and ring fingers webbed; toes irregularly arranged.

CASE 23: Hands show short thumbs; only two phalanges in left index finger; toes webbed.

CASE 24: "Giant great toes and giant thumbs consisting of union of two separate toes and thumbs."

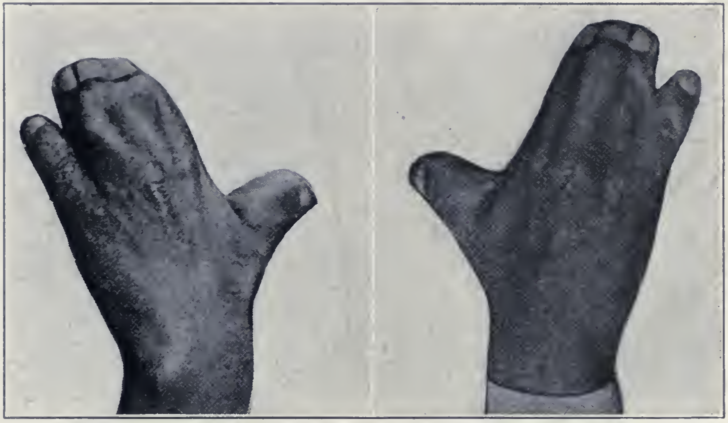

Fig. 15.—Hands of patient of Gadelius seen in Figure 12. (Reproduced from Gadelius.)

In connection with the four cases just enumerated, showing typical malformations of the head and mild degrees of malformation of the hands and feet, should be mentioned the four additional cases probably belonging to the series (Cases 25, 26, 27 and 28). The heads in all four cases were typically acrocephalic. Abnormalities in the arms and legs were noted as follows:—

CASE 25: The great toes were broad and hallux varus was present.

CASE 26: "Peculiar malformation of thumbs: first phalanx curved outward toward the radial side, etc."

CASE 27: Thumbs broad, little fingers kinked, etc.

CASE 28: Elbows cannot be fully extended, etc.

Before leaving the subject of the deformities of the extremities it is most important to point out that the malformations were not limited to the hands and feet in a number of the cases. In the case of Magnan and Galippe, for example, it is stated that complete extension at the elbow joint, supination and certain other movements of the arm were impossible. In the case of Ireland the photograph (Fig. 10) shows that the arms were greatly reduced in length, for the hands reach only to the level of the pelvis.[33] In the case of Camus, there was "synarthrosis" of humerus and radius with hypertrophy of the head of the latter. In the case of Bertolotti and Boidi Trotti there was limitation of movement at scapulohumeral articulations and at elbows (complete extension was impossible), and a synostosis between radius and ulna at the elbow was demonstrated by means of the roentgen ray. In the patient of Dodd and McMullen, the head of the radius became subluxated forward on both extension and supination of the forearm, due, in all probability, as the authors observed, to a congenital defect. In one of the patients of Fletcher[34] (Case 28) the elbows could not be completely extended; the internal condyles were unduly prominent; the heads of both radius and ulna appeared to be thickened and it was impossible to raise the arms to the horizontal.

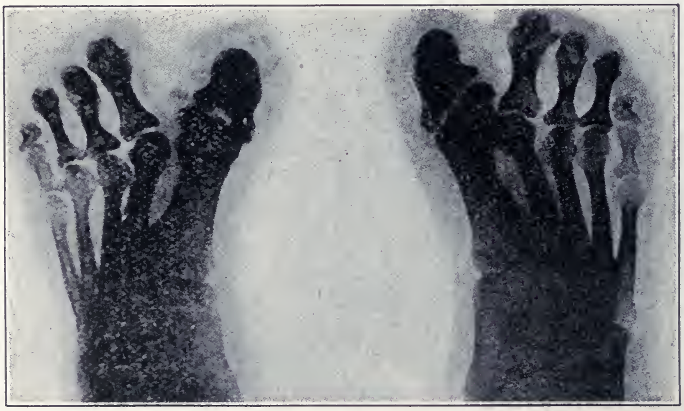

Fig. 16.—Roentgenogram of feet. Patient of Régis, reproduced from Régis to illustrate symmetry of deformity and hallux varus. Age of patient about 16 years. (Case 11.)

The intelligence of the majority of the subjects of the malformation appears to have been normal. In some of them, particularly in those who had found their way into institutions, the intelligence is described as subnormal. Doubtless a number of these latter became institutional inmates as the result of an inability to support themselves on account of the deformities of the extremities, or had been abandoned in early childhood for reason of their unprepossessing appearance.

Physical development appears to have progressed in almost a normal manner. Walking commenced in spite of the deformed condition of the feet at about the eighteenth month.

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[33] We suspect from the appearance of the arms in the photograph that the patient was unable to extend them completely, and in consequence they appear foreshortened.

[34] Fletcher, H. M.: (a) Four cases of oxycephaly, Proc. Roy. Soc. Med., Lond. **2**: Sect. Clin., 113, 1908. Fletcher, H. M.: (b) On oxycephaly, Quart. J. Med. **4**: 385, 1910.

PATHOLOGY

Head: Necropsies were done in only five cases, the two reported by Wheaton (Cases 4 and 5), that of Dubrisay (Case 8), the third of Gadelius' series (Case 16) and the case of Rieping (Case 20). For all useful purposes, however, the number of necropsies amounts only to three, since in Dubrisay's case neither head nor extremities were so much as looked at, and in the case of Gadelius, however complete the examination may have been, the report is limited to the statement that the hypophysis on microscopic examination was normal. Unfortunately, the reports of the findings in the two cases of Wheaton are too fragmentary to be of great value. The main source of knowledge is the report of Rieping.

Wheaton informs us that in both of his cases the posterior fossa was extremely narrow from before backward, and the occipital bones were extremely small. The basi-occipital bone in one case was only one-eight inch in diameter; in the other it was united to the basisphenoid by firm bony union. The bones of the cranial vault presented on their inner surfaces numerous "pits or elliptical depressions," the walls of which were extremely thin, and in some places devoid of calcium. The brain appeared to be compressed and bulged considerably when the dura mater was incised; the convolutions were flattened as if by pressure; yet no accumulation of fluid was present. The anteroposterior diameter of the brain was remarkably shortened in a manner corresponding with the shape of the cranial cavity. There was a marked lack of development of the occipital lobes, which were so small as to leave the cerebellum almost entirely uncovered. The frontal lobes also were small and pointed. No important convolutions appeared to be absent. The description of the fontanels and sutures has already been given.

The contour of the skull in Rieping's case and the condition of the sutures which were open have already been described. The coronal suture was completely synostosed for a distance of 48 mm. on each side of the skull, corresponding to the lower third and part of the middle third of each lateral half. On the inner surface of the skull the site of the synostosed suture was marked by a bony ridge 5 mm. high, continuous with the posterior border of the small wing of the sphenoid. Centering about the middle point of the synostosed portion of the coronal suture on the external surface of the skull was an area resembling a center of ossification but somewhat depressed beneath the level of the surrounding surface. The bone included in this area was considerably thickened. The patent portion of the coronal suture above the synostosis ran in an upward and forward direction instead of pursuing an upward and backward course as under normal conditions. The lambdoidal suture had a more nearly vertical direction than normal. It is not perfectly clear from Rieping's description whether the sphenofrontal and sagittal sutures were partially synostosed or not. The sphenofrontal suture, at any rate, was not well defined either on the external or internal surfaces of the skull, and the sagittal suture was thrown upward into a ridge, forming a typical *crista sagittalis*. The edges of the two parietal bones forming the ridge were apparently locked together and overlapped. No parietal or frontal eminences were present.

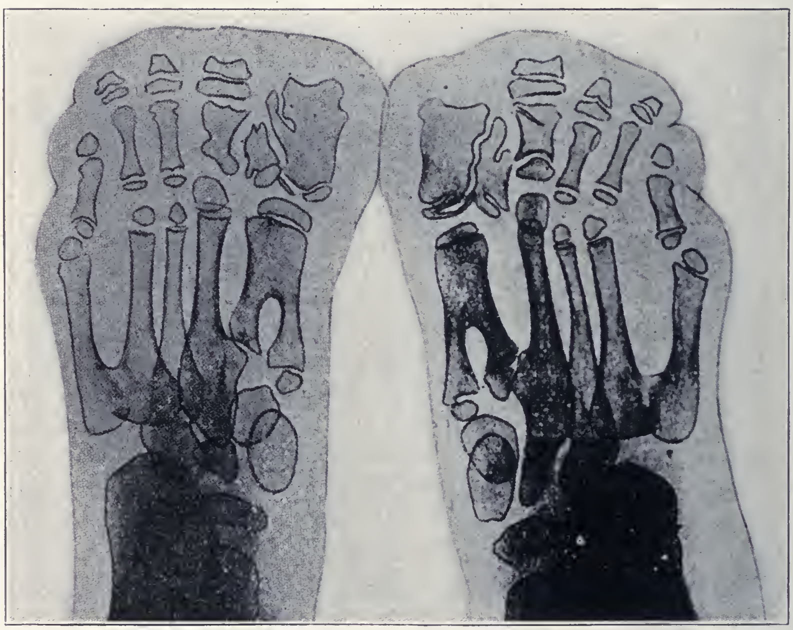

Fig. 17.—Roentgenogram of feet. Patient of Bertolotti and Boidi Trotti, reproduced from Bertolotti and Boidi Trotti to show symmetrical character of malformations. Age of patient, 5 years. (Case 12.)

The base of the skull, as viewed from above, had a rounded rather than an oval form. All three fossae were greatly shortened from before backward, and the two posterior fossae deepened. The anterior fossa was the most abnormal. The small wings of the sphenoid are described as rising upward from the body of the sphenoid like the upstretched wings of a bird. The chief part of the floor of the fossa, that which corresponds to the roof of the orbit, is said to have been more nearly vertical than normal.[35] At the same time it is described as sloping steeply downward to join the lamina cribrosa of the ethmoid. The latter was greatly depressed and lay as it were at the bottom of a valley; it was 58 mm. below the tips of the small wings of the sphenoid as compared with 20 mm., the distance in a normal skull of a new-born child. In the middle fossa the most important feature of the deformity was the anterior position of the great wing of the sphenoid. The great wing was described as being more nearly parallel to the frontal plane than normal. The most striking features about the posterior fossa were its small size and funnel shape. Its walls sloped steeply on all sides into the foramen magnum. The pituitary fossa was larger and deeper than the fossa in the average skull. The lamina cribrosa was still in a cartilaginous condition and the sella turcica in part cartilage.

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[35] Rieping's description of the floor of the anterior fossa is not clear and apparently contains contradictions.

The depth of the orbital cavity was greatly reduced as a result of the downward inclination of the roof of the orbit and the forward position of the great wing of the sphenoid.

The dura, arachnoid and pia were normal.

The shape of the brain conformed to that of the cranial cavity. The cerebellum in comparison with the brain mass as a whole appeared small. An internal hydrocephalus of moderate degree was present.

Certain negative features were of moment. There was no evidence of any inflammatory condition in the membranes or bone. The optic foramen was not narrowed. There was no synostosis noted at the base. There were no digital impressions on the inner surface of the skull. The size of the sphenoidal angle was not mentioned.

The roentgenograms[36]. demonstrate in a striking manner the abnormal shape of the skull, its height, breadth, shortness, the abrupt ascent and lack of curvature of the tabella of the occipital bone, the upward and slightly forward slope of the frontal. They also furnish new data. Most important, they show that there is diminution in the density of various portions of the calvarium and that digital impressions are present. In some portions of the calvarium the digital impressions appear as they actually are, that is, as circular or elliptical pits. In the frontal and occipital regions, however, where the planes of the bony walls are perpendicular or almost so to the plate, the digital impressions appear as wavy branching lines. In the case of Bertolotti and Boidi Trotti and in our case they were most numerous in the frontal region; in other cases they were found chiefly in the occipital and parietal regions.

Roentgenograms of the head also revealed that the posterior and middle cerebral fossae were not only shortened in their antero-posterior diameter but were abnormally deep. Bertolotti and Boidi Trotti state that in their case roentgenological study proved the length of the anterior cerebral fossa to be reduced and the orbital cavity to be shallower than normal. In both Bertolotti and Boidi Trotti's case and our own the roentgenograms of the head showed at the site of the spheno-occipital synchondrosis a dark bandlike shadow, proving that the synchondrosis between the basi-occipital and sphenoid bones had not yet disappeared, that is, the basi-occipital and basisphenoid were still ununited. They supplied evidence also of the existence of a "basilar lordosis" as shown by an increase in the size (in the obliquity) of the sphenoidal angle.

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[36] Roentgenograms of the head are available in the reports of Davis, Bertolotti and Boidi Trotti, and Powers and Park; Ruh and de Salterain refer to roentgenograms of the head but do not exhibit them.

Extremities: Although no dissection of the extremities in any of the cases has been made, the roentgenograms reveal conditions in the skeletal elements with a clearness equal to that of anatomical preparations. We shall point out merely the principles that seem to underlie the malformations of the hands and feet (Figs. 8, 9, 16, 17).

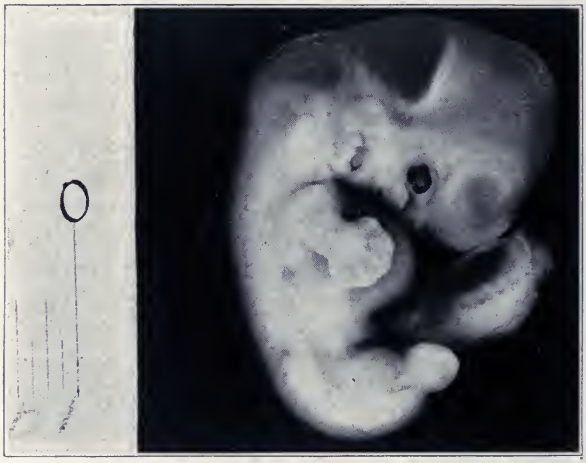

Fig. 18.—Photograph of embryo No. 1909 of the Carnegie Embryological Collection. Crown-rump length, 14.6 mm. Estimated menstrual age, 46 days. Outline of blastemal skeleton in hand plate clearly visible to naked eye. Development in foot plate not so advanced as in hand plate. (Courtesy of Dr. Streeter.)

In general it may be stated that:

(1) The maldevelopment of the hands and feet was not limited in any instance of which there are roentgenographic records to the soft parts alone but involved also the bones.

(2) The maldevelopment was more extensive in the distal portions of the extremities than in the proximal and reached its maximal development in the extreme ends.[37]

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[37] In one case there was limitation of movement at the scapulohumeral articulation, in seven cases at the elbow (in only two cases was there roentgenographic proof of malformation of the bones at the elbow). In all cases the bones of the hands and feet were malformed and in all cases the phalanges were more extensively malformed than the metacarpals. In all the cases with the exception of one (Case 12, Bertolotti and Boidi Trotti) the most marked malformation was to be found in the terminal phalanges of the hands.

(3) The malformation was more extensive in the upper extremity than in the lower.

(4) The malformations were bilateral.

(5) In the arrangement of the malformed parts on the two sides of the body there was exhibited a strong tendency toward symmetry. (In several cases the shadow of the intricately deformed skeleton of the hand or foot on one side was almost the mirror image of the shadow of its fellow on the other (Figs. 16 and 17). In all cases there was a correspondence in the finer details on the two sides of the body that was remarkable (Fig. 8, i and ii, vi and vii; Fig. 9).

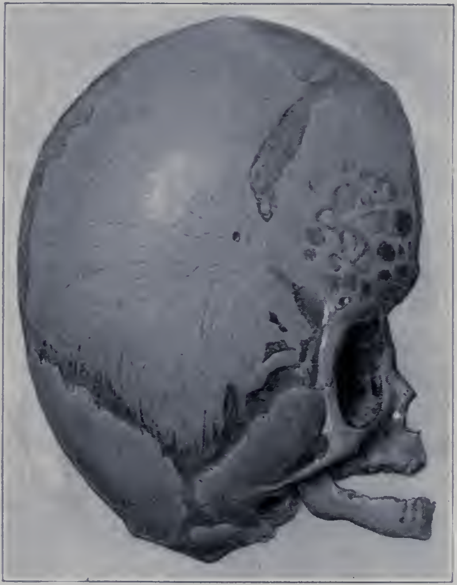

Fig. 19.—Acrocephalic skull of new-born child, lateral view, reproduced from Zuckerkandl, showing synostosis of less than one third of coronal suture. The nonsynostosed parts of coronal suture are widely separated. Just posterior to the synostosed portion of the coronal suture, lying in the parietal bone, is an area of thickened bone with radial striations resembling a center of ossifications. Extreme degree of convolutional atrophy.

(6) The malformations consisted essentially not in new formations but in the absence or imperfect development of certain elements, namely, the structures forming the joints, the soft tissues interposed between the bones, etc., in the union of bones, and in alterations in form and size.

The malformations showed certain special features that must be pointed out. In all cases except two (Case 11, Régis; Case 14, Gadelius [Fig. 8, i *b*]), the joints between metacarpal bones and the proximal phalanges were preserved. In all cases except one (Case 12, Bertolotti and Boidi Trotti (Fig. 8, viii), so far as it is possible to determine from the roentgenograms, the bones of the carpus and tarsus remained ununited. The integrity of the thumbs and little fingers was more often preserved than the integrity of the intervening fingers; that is, the thumbs and little fingers exhibited less tendency toward cross union, both osseous and through the intermediary of the soft parts, than the middle three fingers. In all cases there was evidence of defective development in a quantitative sense; that is, in all cases there could be found phalanges that seemed shorter than normal (Fig. 8, *l*) or thinner than normal (Fig. 8, *k*) or phalanges were absent or cross union of phalanges or metacarpal bones with obvious reduction in substance existed (Fig. 8, *h*). In two cases (Case 12, Bertolotti and Boidi Trotti; Case 13, Davis) there was said to be evidence of reduplication of osseous elements (Fig. 8, viii). In some of the cases metacarpal bones or phalanges could be found which appeared to exceed the normal in thickness (Fig. 8, *j*). In general, if an excess of substance existed, it appeared to be in an increased thickness; if a deficiency of substance existed, it seemed to consist in a decreased length or in decreased thickness where a fusion-like union with a neighboring bone had taken place. The impression was obtained that the deficiencies in osseous substance predominated over the excess. In a number of the cases bones were abnormally shaped, even though no synostosis existed (Fig. 8, *m*).

The following types of union of metacarpal bones and phalanges could be distinguished:

1. Union of phalanges with their fellows of the same fingers.
    (a) Union with apparently almost complete preservation of cleft corresponding to joint—possibly fibrous union (Fig. 8, *a*).
    (b) Union of one phalanx with another with partial preservation of cleft corresponding to joint (Fig. 8, *b*).
    (c) Complete union with formation of ridge or enlargement at site of junction (Fig. 8, *c*).
    (d) Complete osseous union of such nature that united bones appear as one bone (Fig. 8, *d*).
    (e) Complete union with formation of heterogeneous mass (Fig. 8, *e*).
2. Cross union between metacarpal bones and between phalanges.
    (f) Side to side union, the outline of each bone remaining distinct—fibrous union (?) (Fig. 8, *f*).
    (g) Partial osseous union through bridge formation (Fig. 8, *g*).
    (h) Complete fusion with reduction of substance but retention of form (Fig. 8, *h*).
    (i) Complete fusion into heterogeneous mass (Fig. 8, *i*).

VIEWS CONCERNING THE ETIOLOGY OF THE DEFORMITIES AND THE RELATION OF THE DEFORMITIES OF THE EXTREMITIES TO THOSE OF THE HEAD

Several authors have attributed the malformations of both head and extremities to fetal syphilis; Maygrier and Fournier because of the history of two miscarriages and the admission of a syphilitic infection on the part of the father sixteen years previous to the birth of the patient; Dubrisay on account of a history of a miscarriage and an ulceration of the genitalia, and deSalterain in spite of the absence of any history suggesting syphilitic infection and of a negative Wassermann reaction of the blood. Because of " 'snuffles,' the earthy complexion, shriveled skin, fibrous thickening of the spleen" and "elliptical patches of atrophy or defective ossification of the cranial bones, and their softness during life, together with the irregular crenated edges of the bones bounding the sutures and fontanels," Wheaton expressed the opinion that the malformation of the head had been caused by fetal syphilis in both his cases.[38] Curiously enough, he regarded the malformations of the hands and feet as the effects of compression by amniotic adhesions. The amniotic adhesions, however, he thought in all probability of syphilitic origin.

Magnan and Galippe declared the malformation of the head in their case to have been caused by an inflammatory process at the base of the skull. They did not attempt to define its nature and offered no explanation for the deformities of the extremities and did not seek to bring them into causative relationship with the deformities of the head.

Although Bertolotti and Boidi Trotti referred the malformation of the head to an "abnormal disposition of the germinal layers in early embryonic life," [39] they proposed an entirely different explanation for the deformities of the extremities; according to it the deformities of the extremities were the result of maldevelopment of the skull. In order to make clear Bertolotti and Boidi Trotti's opinions concerning the relationship of the deformities of the extremities to those of the skull as well as the views expressed by other writers, it is necessary to give a brief exposition of the theory propounded in 1904 by Babes.[39a]

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[38] Wheaton remarks: "I am therefore of opinion that the cranial deformity in these cases is due to fetal syphilis, although no clear history of syphilis in the parents of the infants could be obtained."[17] p. 240.

[39] The views of Bertolotti and Boidi Trotti concerning the origin of the malformation of the head are not entirely clear. The inference from the above quotation is that the two authors considered the malformation of the head as germinal in origin or as acquired very early in fetal development. On the other hand, they refer to a fetal synostosis of the metopic suture occurring "in the third and fourth months of fetal life" and also of the sphenofrontoparietal sutures as if the mal-development of the skull had originated with them. In a previous publication[12]a Bertolotti very decidedly took the view that oxycephalic malformations were rachitic in origin.

[39a] Babes, V.: (a) Ueber Gesichtsanomalien, welche eine Umwandlung der Extremitäten (Akrometagenese zur Folge haben), Berl. klin. Wchnschr. **41**:464, 1904. (b) Sur certaines anomalies congénitales de la tête, déterminant une transformation symétrique des quatre extrémités (acrométagenèse), Compt. rend. Acad. d. sc. **138**: 175, 1904.

In the course of examination of a series of monsters Babes observed that malformation of the extremities occurred when the base and upper parts of the facial portion of the skull were defectively developed, but not when the malformation was limited to other parts of the skull. Using Babes' own terminology, aprosopia, schistoprosopia, certain forms of cheilognathopalatoschisis, in which the base of the skull was affected, and hydrocephalus with premature ossification and sclerosis of the base of the skull were accompanied by ectodactyly, polydactyly, syndactyly, or shortening or lengthening of an extremity, single finger or toe, or by combinations of these, whereas less severe types of deformity of the skull in which the base and upper part of the face remained unaffected, were unaccompanied by malformation of the extremities. Babes concluded that there must exist in the region of the base of the skull and the facial portion of the cranium a trophic center that controlled the normal growth of the extremities. When this trophic center was absent or imperfectly developed, growth of the limb buds became abnormal. As to the location of the center Babes is not clear. He writes as if he thought it is situated in the base of the skull, but at the same time seems to permit the implication that the center may be in the hypophysis or base of the brain.

Stimulated by Babes' theory, Bertolotti and Boidi Trotti attributed the deformed condition of the extremities to a disturbed function of the hypophysis, the result of a maldevelopment consequent to the malformations of the skull. None of the authors of the case reports other than Bertolotti and Boidi Trotti seem actually to have espoused Babes' theory. Two of them, however, may be said to have flirted with it. Apert refers to it as "the most satisfactory" theory and as being "alluring and agreeing well with what the study of acromegaly has taught concerning the trophic rôle of the pituitary gland in relation to the extremities." Ruh refers to it as "one of the most attractive theories for the explanation of certain forms of atypical development."

Gadelius seeems to have lent a willing ear to the theory that a defect in the fetus' own organs of internal secretion was responsible for the malformation of both extremities and head.

Rieping considered the malformation of the head as germinal in origin. The malformation of the extremities also, he seems to have regarded as germinal. Apparently, however, he did not think that any special association existed between the malformations of head and extremities. He held that oxycephaly was a malformation especially prone to be accompanied by "other congenital malformations" and seems to have thought that the occurrence of symmetrical syndactylous deformities in his case was accidental.

To whatever extent the various authors may have differed in regard to the origin of the deformities of the skull or the relationship of the deformities of the skull and extremities to each other, all, with the single exception of Rieping,[40] seem to have agreed that the pathologic process at the base of the deformity of the skull was a premature synostosis of the cranial sutures.

Such are the facts relating to the cases exhibiting this curious combination of congenital anomalies and such the ideas expressed concerning them. We shall endeavor to show that the theories advanced in regard to etiology are untenable and shall seek to extend knowledge one step further.

SYPHILIS AS THE CAUSE OF THE MALFORMATIONS

Although there can be no doubt that malformations like those described may occur in subjects of congenital syphilis, it is scarcely necessary to bring forward arguments to prove that they are not syphilitic in origin. Fetal syphilis does not manifest itself by the production of isolated congenital malformations. While the Wassermann reaction has been furnishing repeated demonstration that congenital defects such as spina bifida, cleft palate, polydactylism, etc., are not syphilitic in origin, studies in heredity and experimental teratology have thrown light on their true sources of origin.

The symptoms and pathologic changes, almost all of them irrelevant, cited by Wheaton in favor of the existence of congenital syphilis, the meagre evidence supplied in the histories of the cases of Maygrier and Fournier, and of Dubrisay, at most suggest the possibility that congenital syphilis was present. In not one case of the entire series is there the record of any pathologic condition actually indicative of congenital syphilis, and in each case in which the Wassermann test was done (cases of Davis, Ruh, de Salterain, Powers and Park) it was negative. It is possible to exclude syphilis as the etiologic factor.

THE DEFECTIVE DEVELOPMENT OF THE EXTREMITIES NOT SECONDARY TO THE DEFECTIVE DEVELOPMENT OF THE SKULL

The theory offered by Babes rests on three hypotheses, each of which requires separate proof, (1) that the growth and development of the extremities are governed from a center; (2) that the center is situated in the base of the skull, or allowing Babes' theory the widest possible interpretation, in the contiguous portion of the brain, or in the hypophysis, and (3) that it is wanting or functionally impaired in severe malformations involving the basal region of the skull. There can be no doubt that cleft palate in its severe forms and hydrocephalus accompanied by "premature ossification and sclerosis of the base of the skull" (Babes means cases ordinarily described as acrocephaly or oxycephaly) are much less frequently accompanied by "ectodactyly, polydactyly, syndactyly," etc., than by normal conditions of the extremities, and that, conversely, deformities of the extremities occur in by far the majority of instances in persons having normal craniums (namely, the numerous examples of familial polydactylism and syndactylism). Becase phenomena occur in combination, it in no wise follows that the relationship between them is one of cause and effect. Indeed, if their occurrence in combination is inconstant, if each happens independently of the other, the relationship between them cannot have a casual basis. We shall attempt to point out the incorrectness of Babes' theory, however, in other ways.

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[40] Rieping's views will be discussed later (pages 283, 284).

The fact that the growth and development of the limb buds of the embryo is not dependent on formative stimuli emanating from the central nervous system has been indicated by accidents of development and experiments. As an example of accidents of development may be mentioned the oft cited anencephalic human monster without spinal cord or motor nerves but with normal peripheral sensory nerves, muscles and skeleton, described by Leonowa.[41] The monster had a body length of 34 cm. The absence of anterior horn cells and of the anterior nerve roots was determined by microscopic examination. Other similar anencephalic amyelic monsters have been described (Herbst [42]). As a matter of fact, the discussion has raged not concerning the dependency of the osseous system for its development on the integrity of any part of the nervous system, but the dependency of the muscular system for its development on the integrity of the motor nerves. There has never been reason to assume, so far as we are aware, that the development of the skeleton was determined by nervous influences. Weber,[43] himself, has described an amyelic calf fetus with normally developed skeleton in support of the theory of a neurogenic origin for the muscular system. In the new-born calf in question the larger part of the vertebral column and the spinal cord from the level of the first thoracic vertebra was absent. Though the muscles of the hind legs were lacking, the hoofs, as well as the bones, were normally developed.[44]

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[41] von Leonowa, O.: Ein Fall von Anencephalie combinirt mit totaler Amyelie, Neurol. Centralbl. **12**: 218, 1893.

[42] Herbst, C.: Formative Reize in der tierischen Ontogenese. Ein Beitrag zum Verständnis der tierischen Embryonalentwicklung. Leipzig, 1901, A. Georgi, p. 125.

[43] Weber, E. H.: Ueber die Abhängigkeit der Entstehung der animalischen Muskeln von der der animalischen Nerven, erläutert durch eine von ihm und Eduard Weber untersuche Missbildung, Arch. f. Anat. Physiol. u. wissensch. Med., 547, 1851.

[44] The joints were ankylosed apparently from disuse.

The experiments referred to, indicating that the limb buds are not dependent on nervous impulses for the assumption of normal form, are those performed by Harrison[45a, b] on frogs. Harrison removed the spinal cord in a series of frog embryos before histologic differentiation had occurred in either the muscular or nervous systems, so that the isolation from the central nervous system of the cells that were to enter into the formation of the limb buds was complete, and any formative stimuli arising from the central nervous system were eliminated. The limb buds thus freed from all nervous influences differentiated normally. Harrison transplanted the limb buds of frog larvae before the nerves of the body had grown into them, so that, when a connection with the central nervous system became established, it was an abnormal one. Yet the identity of the limb was preserved.

Although we cannot offer evidence as striking as that contained in the work of Harrison to prove that growth and development of the limb buds is not determined by any organs or combination of organs of internal secretion of the fetus, we can bring forward considerations sufficient to render any such view extremely improbable. All facts at our disposal indicate that the embryo is dependent for his proper growth and development not on his own but on the parental organs of internal secretion. Though the medical literature is full of examples of abnormal conditions attributed to disturbances in the fetal organs of internal secretion and abounds in explanations of congenital defects and disease on the basis of insufficiency in the fetus' own endocrine glands, there is not one single pathologic condition which in the present state of our knowledge can be referred to that cause with any justification whatsoever. Furthermore, clinical observation teaches that disturbances in the function of the endocrine glands may give rise to changes in the body as a whole or at least in a variety of tissues (gigantism, acromegaly, dystrophia adiposogenitalis, myxedema, hyperthyroidism, eunuchism) or to altered metabolic states such as those seen after removal of the pancreas or parathyroids, but gives no indication that they produce alterations in parts of the body which are composites of tissues, such as the head, extremities, etc., to the exclusion of other parts. It is impossible to conceive that an organ of internal secretion can cause changes to occur in the bone, muscles, connective tissue, fat and integument of certain divisions of the body and not act at all on the same tissues elsewhere.

In the single case in which the hypophysis was examined (Case 16, Gadelius) it was reported normal.

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45. Harrison, R. G.: (a) An experimental study of the relation of the nervous system to the developing musculature in the embryo of the frog, Am. J. Anat. **3**:197, 1904. (b) Experiments in transplanting limbs and their bearing upon the problems of the development of nerves, J. Exper. Zool. **4**: 239, 1907. (c) Experiments on the development of the fore limb of Amblystoma, a self-differentiating equipotential system, J. Exper. Zool. **25**: 413, 1918.

The third possibility implied in Babes' theory, that a center exists in the undifferentiated tissue of the base of the skull, which presides over the growth and development of the extremities, it is not necessary to consider.

It is possible to conclude that the defective development of the extremities is independent of the defective development of the skull. From this fact it follows either that the malformations of skull and extremities have no relationship to each other or else have a common origin.

EVIDENCE OF THE EARLY ORIGIN OF THE DEFORMITIES OF THE EXTREMITIES

We might have pointed out that the deformities of the extremities dated back to an extremely early period of fetal development, before ossification had taken place anywhere, as final evidence that they could not have been caused by a defective development of the bony cranium. We now bring forward the reasons for believing that their origin was an early one but with a different object in view, namely, to shed light on the pathological condition at the basis of the cranial malformation and the period of fetal development at which it already was or became established. That the deformities of the extremities were in existence at an extremely early period of fetal development cannot be doubted after the facts relating to the normal development of the extremities are recited.

The arm bud makes its appearance about the third week of embryonic life (in an embryo 2.1 mm. long) and reaches considerable size by the fourth week.[46] In the fourth week (embryo 7 mm. long) differentiation begins to occur in the form of an increased condensation of the mesenchyme known as the skeletal core and representing the humerus, radius and ulna. The membranous radius and ulna are continuous proximally with the membranous humerus, and the membranous ulna, larger than the radius, appears to be more directly the continuation of the humerus. Distally the radius and ulna pass into an ill defined mass of mesenchyme which is the hand plate. No cartilage is yet present. By the fifth week (in an embryo 11 mm. long) the skeletal core can be differentiated into several of its elements, three of which, the humerus, radius and ulna, now contain in their central portions cartilage. By this time centers of condensation of the mesenchyme can be distinguished in the hand plate corresponding to the scaphoid, semilunar, cuneiform, trapezoid, trapezium, os magnum, and unciform bones. From these centers five cores of condensed mesenchyme radiate outward toward the end of the arm bud, but shade off distally into undifferentiated mesenchyme; they are the future metacarpal bones. At the end of the sixth week (embryo 16 mm. long) (Fig. 18) most of the skeletal elements of the arm have passed over into cartilage. The five metacarpal bones at this stage appear as slender cartilages surrounded by very thick condensed mesenchymal tissue, forming the perichondrium. The ulnar four phalanges of the first row, having passed the mesenchymal stage of development, appear as short slender cartilages deeply imbedded in condensed mesenchymal tissue. The proximal phalanx of the thumb is still composed of condensed mesenchyme. By the end of the seventh week (embryo from 18 to 20 mm. long) all the skeletal elements of the arm are cartilaginous, except the distal row of phalanges from the second to the fifth digits, which are still of condensed mesenchyme. All the muscles of the arm can now be recognized and the tendons and ligaments are well formed.

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[46] This description of the development of the arm bud is taken from that given by Lewis.[47]

[47] Lewis, W. H.: The development of the arm in man, Am. J. Anat. **1**: 145, 1902.

Separation of the humerus, radius and ulna and of the bones of the wrist and hand with the formation of joint cavities does not occur until the third month of fetal life.

The development of the lower extremity is identical in principle with that of the uppper extremity. Differentiation begins a little later, however, and the development does not proceed quite so rapidly (Fig. 18).

The points which we have wished to emphasize in the description just presented are these: Differentiation of metacarpal bones and phalanges involving separation from their neighbors can be seen as early as the fifth and sixth weeks of embryonic life, before they contain bone or cartilage, when they still consist of mesenchyme. At this early period of development, humerus, radius and ulna, carpal bones, metacarpal bones and phalanges, are continuous with each other, and form what might be termed a single branch or tree.

The account of the development of the arm just given furnishes strong evidence in favor of the early origin of the deformities of the extremities. Since metacarpal bones and phalanges exist separately from their fellow in the fifth and sixth weeks of embryonic life in embryos 11 mm. long, it is almost certain that the deformities of the hands, characterized by *union* of metacarpal bones and phalanges with their fellows must have been in existence at that early period.

The malformations of the skeleton of the hands and feet, as revealed by the roentgen ray, show peculiarities which seem to preclude an origin in an inflammatory process in the ordinary sense after blastemal differentiation had once taken place. It is necessary to point merely to the almost mirror image symmetry demonstrated in the roentgenograms of the hands and feet in the patients of Bertolotti and Boidi Trotti (Fig. 17), Régis (Fig. 16) and the authors (Fig. 9); to such curious formations as the bridge of bone connnecting the middle phalanges of the index and ring finger on the hand (Fig. 8, ii g) or the island of bone lying in the concavity of the bony mass representing the two phalanges of the great toe (Fig. 8, ix) in the first case of Gadelius' series (Case 14); and, finally, to the marked hallux varus, apparently present in all cases.

In the light of the history of the development of the normal arm it seems reasonable to think, therefore, that the mesenchymal cores representing the metacarpal and metatarsal bones emerged from the solid masses of the hand and foot plates connected together at various points instead of separate and that the fingers and toes budded out united and with their skeletal cores joined together at the tips or along the sides or by means of transverse bridges, or fused. The transverse zones of less condensed mesenchyme, which mark off one phalanx from its fellow of the same finger and become the sites of subsequent joint formation, in many places did not develop at all or developed incompletely. In the case of Bertolotti and Boidi Trotti in which there was ankylosis of humerus with ulna and head of ulna with head of radius, the skeletal core representing the humerus was presumably continuous with the skeletal cores representing radius and ulna, and the skeletal cores representing radius and ulna were presumably joined together in their upper part. And, finally, in those cases in which there was limitation of motion at the elbow joint, the arrangement of the mesenchymal elements was probably such that, when at a subsequent period of development separation of humerus on the one side and radius and ulna on the other took place, it was an imperfect separation with the production of an imperfect joint like some of the imperfect joints in the fingers and toes.

ASSOCIATION OF DEFORMITIES OF SKULL AND EXTREMITIES NOT MERE COINCIDENCE

Since there is good ground for thinking that the defective development of the extremities was present at an extremely early period of fetal life, it would seem reasonable to suppose that the defective development of the skull dated from the same early period. Before any such inference can even be considered, however, it is necessary to give reasons for believing that the association of the deformities of skull and extremities was not mere coincidence, but that a relationship of some kind existed.

If the association between the deformities of the skull and extremities had been entirely accidental, it should be possible to find a variety of congenital anomalies such as spina bifida, malformation of the heart, polydactylism, extrophy of the bladder, hydrophthalmus, etc., existing in single combination with acrocephaly, and these should occur with a frequency corresponding to the rate of incidence of each. But so far as we can determine, acrocephaly recurs repeatedly in single combination with the type of defective development of the extremities described and with other congenital anomalies, rarely, if at all.[48] Symmetrical polydactylism is said to be more frequent than symmetrical syndactylism; yet the malformation of the skull which characterizes our series of cases occurs with symmetrical syndactylism but not with symmetrical polydactylism.[50]

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[48] The following case reports by Carpenter[49] relate to three children in one family, each the subject of malformations of head and extremities and also other congenital defects . We probably should have included them in our series of cases of acrobrachycephaly with defective development of the extremities. We did not do so because of the absence of an exact correspondence in the malformations of both head and extremities to those in our series. The congenital malformations in the cases in question were probably germinal in origin. The facts that a cousin of the three malformed children had malformed hands and that the malformations exhibited such fundamental similarities in all three children are the points indicative of an origin in defective germ plasm rather than of an acquired origin.

F. H.—Parents not deformed. A brother of the mother had a child with malformed hands, but without deformity of the skull. "No history of syphilis." Six pregnancies. The first two resulted in the births of the subjects of Case Reports 1 and 2, the third in the birth of a normal child, the fourth in the birth of a still-born child, said to have resembled the first two children, the fifth in the birth of a normal child, the sixth in the birth of the subject of Case 3.

CASE 1.—Girl, aged 1 year, 11 months, when examined, showing deformities of the head described as follows: "Her frontal bone rose walllike, and it was on a level with the tip of her nose. Looked at from the front the forehead was pear-shaped, with the stalk of the pear at the root of the nose, and its base passed into a beak of bone. The sagittal suture passed forward for some distance in the usual direction until within a finger's breadth of the coronal suture. Here a distinct, beaklike, bony prominence . . . was encountered which ran forward for about three inches. The beak was one inch broad at its widest part, and one-half inch at its narrowest. The sagittal suture bifurcated at the commencement of this bony prominence, and on either side of it sutures could be felt. Behind the level of the coronal suture there was three-quarters inch of beaklike prominence of bone, and in front the beak merged into the base of the pear-shaped frontal protuberance of the skull. . . . The posterior and posterolateral fontanels were patent. The skull was bulged on either side above the level of the zygoma, which ended about two fingers' breadths on either side of the median beak of bone. The root of the nose was flat, the upper lids were thrust down, and also the eyes." The little and first fingers and the thumbs were partially and the ring and middle fingers completely webbed. There were six toes on each foot, all webbed completely except the little and fourth toes, where the webbing was only partial. In addition to the abnormalities mentioned, a congenital malformation of the heart apparently existed, and a hernia of the abdominal wall.

CASE 2.—A girl, aged 3 years, 10 months, when examined, had a forehead somewhat like that of patient of Case 1. The forehead, however, did not overlap the tip of the nose. The skull was keel-shaped. The keel commenced at the top of the forehead and terminated above the parietal eminences. The back of the head was normal. Circumference of skull 18 inches. The eyes were prominent with heavy upper lids. The cornea was imperfectly developed, at one portion its outlines were not elliptical and the neighboring sclerotic seemed to run into the cornea. The photograph accompanying the case report indicates that the aperture of the lids was set obliquely in a downward and outward direction. The nose was short and the bridge flattened. The hands showed the same deformity as the hands of the patient of Case 1. There were six toes on each foot. The big toes and the next were partially webbed. There was incomplete webbing between the little toes and the next, and the webbing was complete in the others. An umbilical hernia was present, and a congenital malformation of the heart was thought to exist. The patient met an accidental death, aged 10.

CASE 3.—A boy aged 5 weeks. The skull, looked at from the front, was diamond-shaped; when viewed from the side, the forehead sloped backward in a straight line from the tip of the chin to the top of the skull. The occipital bone was thrust forward, with the result that the union of the occipital and frontal bones formed the peak of the skull. The eyes protruded frog-like, the eyeballs being kept in position merely by the lids. It was possible readily to dislocate the globes, so that they hung suspended by their muscular and nerve attachments. The circumference of the skull was 17 inches; the greatest anterior posterior 6½ inches, the greatest breadth 6½ inches; from the root of the nose to the back of the skull 5 inches. The middle and third fingers of each hand were webbed to the base of the nails. There were six toes on each foot all directed inward; the three inner on each foot were webbed. Each toe contained two phalanges, the proximal being long and evidently corresponding to the proximal and middle. There was also a hernia through the linea alba.

[49] Carpenter, G.: (a) Two Sisters Showing Malformations of the Skull and Other Congenital Abnormalities, Rep. Soc. Study Dis. Child., Lond. **1**: 110, 1900. (b) Case of Acrocephaly, with Other Congenital Malformations, Proc. Roy Soc. Med., Sect. Dis. Child. **2**: 45, 1908.

It seems most unlikely, therefore, that the association between the deformities of the head and of the extremities was merely the coincidence in one person of morbid phenomena entirely unconnected with each other. A relationship of some kind must have existed betweeen them. Either the two malformations had a common origin in defects in the germ plasm or else they were acquired together in the course of intra-uterine development from some common source.

Rieping's view, that the occurrence of syndactylous deformities of the extremities in conjunction with the malformation of the head had no special significance, was apparently formed in ignorance of the existence of the entire series of cases of the present report.

THE MALFORMATION OF THE HEAD

The malformation of the head exhibits several fundamental resemblances to the malformations of the extremities. At the same time, it shows certain differences. These differences, apparently, can be explained on the ground of the peculiar relation of the cranium to the growing brain. Because the brain is bound to fulfill its inherent demand for growth, a factor is introduced into the production of the cranial deformity, for which no counterpart exists in the case of the extremities, namely, intracranial pressure. The subject of the intracranial pressure and the rôle which it plays in the production of the cranial deformity will be discussed subsequently.

Unfortunately, the roentgen ray does not resolve the complex malformation of the skull into its parts like the deformities of the extremities. The two necropsy reports of Wheaton supply little information that cannot be supplied from other sources. The necropsy report of Rieping is the sole reliable source of information. In view of the dearth of facts, it is necessary to use indirect methods of investigation, and to apply to our cases the pathologic findings of others in kindred malformations of the skull uncomplicated by malformations of the extremities.

IS THE PART OF THE SKULL DERIVED FROM CARTILAGE THE ONE PRIMARILY AFFECTED?

The chief portions of the skull derived from cartilage are the ethmoid, the body, small wings and parts of the great wings of the sphenoid, the basilar process of the occipital and greater part of the tabula below the superior curved line and the petrous portion of the temporal bone. These parts of the skull, with the exception of the tabula of the occipital bone, virtually form the base. Perhaps, the most important part of the base from the standpoint of the development of the skull as a whole is the axial portion. It extends from the nose to the foramen magnum, and is formed entirely of bones laid down in cartilage. It consists of the basilar process of the occipital, the body of the sphenoid and the ethmoid. *Is there evidence to show that the base of the skull, or more particularly the axial portion, is the part primarily affected?*

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[50] If the data were available, with little doubt it would be possible to offer statistical proof that the relationship between the two deformities could not consist in a mere coincidence of unrelated phenomena. For example, if symmetrical syndactylous deformities of the extremities occurred once in every 1,000 births and acrocephaly once in every 1,000 births, the combination ought to occur once in every 1,000,000 births, and one case of acrocephaly with syndactylism ought to occur for every thousand cases of acrocephaly alone. It seems probable that the incidence of the deformities in combination is altogether too frequent as compared with the incidence of acrocephaly alone to permit of the possibility that the occurrence together was accidental.

With the exception of Bertolotti and Boidi Trotti and Rieping, all authors who have given any opinion, have referred the primary defect to the base. The only good reason,[51] however, for thinking the primary defect basal was that Wheaton found an underdevelopment of the basilar portion of the occipital bone in one of his two cases and closure of the suture between the basilar processes of occipital and sphenoid bones in the other.

Rieping, on the contrary, proved by necropsy that the base of the skull was not defectively developed in his case. In Bertolotti and Boidi Trotti's patient roentgenograms showed the basilar portions of occipital and sphenoid bones to be ununited. In our patient also, roentgenographic study revealed that the basilar processes of sphenoid and occipital bones were still separate and comparative measurements made from roentgenograms of the skulls of normal children failed to indicate any reduction in the distance between basion and the anterior clinoid processes or in the length of the axial portion of the skull.

We may conclude that, though the base of the skull may have been primarily involved in some cases of the series, it was not directly affected in all. It is certain that the malformation of the skull could not have been limited to a defective development of its cartilaginous portions in any one of the cases.

IS THE PART OF THE SKULL DEVELOPED FROM MEMBRANE THE ONE PRIMARILY AFFECTED?

In several of the cases there was evidence of defective development of parts of the skull derived from membrane in the presence of clefts of the bony palate.[52] Camus, Magnan and Galippe, and Bertolotti and Boidi Trotti described the superior maxillary bones in their patients as actually atresic. It becomes almost certain, however, that parts of the skull formed in membrane were primarily affected in every case of our series as the result of a comparison of the deformities of the head with those in chondrodystrophy.

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[51] The greatly increased vertical and lateral diameters and decreased anteroposterior diameter would seem to indicate an obstruction to growth in the anteroposterior diameter. The open fontanels and sagittal and metopic sutures would seem to imply that the obstruction to growth was at the base, on the ground that the vertex was free. The knowledge that the axial portion is the first part to be differentiated and the rest of the skull is formed around it as around a central shaft renders it easy to understand how defective formation of the axial portion might account for extensive alterations in all other parts. Finally, the involvement of the bones of the extremities, which are derivatives of cartilage, suggests that the base of the skull was the part affected on account of its cartilaginous origin. It must be apparent that the arguments just presented in favor of the view that the base of the skull was primarily involved are merely suggestive.

The peculiar form of the skull in chondrodystrophy depends on the defective development of the cartilaginous derivatives, especially those forming the axial portion, and the unrestricted development of those parts derived from membrane. If the cartilaginous portions of the skull were the only parts affected and the portions laid down in membrane remained entirely normal, the deformity of the skull ought to bear a similarity to the deformity in chondrodystrophy. This is far from being the case, however. In chondrodystrophy the occiput is especially prominent and the voluminous cranial vault bulges outward in all directions. The top of the head is evenly rounded. The fontanels occupy their normal situations and preserve their normal relations in respect to size and shape. The sutures of the vault are normal. In the malformation of the skull under consideration, on the contrary, the occiput is almost flat and the cranial vault does not bulge. The top of the head is peaked. The fontanels occupy abnormal situations and exhibit marked variations in respect to size and form. Some of the sutures of the vault are prematurely closed; others widely open. All these points of difference indicate that the defective development in our cases was not limited to the base alone. The peculiarities in the shape of the head point to a defective growth above the level of the base of one or more of the bones forming the sides of the cranial vault.

As a matter of fact, in six cases of our series there is evidence that the cranial vault was abnormal. Rieping found fusion of frontal and parietal bones and a pathological condition of the sagittal suture with the formation of a ridge. Wheaton described the "occipital portion of the skull" as defectively developed in his two cases. Bertolotti and Boidi Trotti noted a ridge at the site of the metopic suture and thought that premature closure of the coronal and sphenofrontal sutures was demonstrated by the roentgen ray. Ruh observed a ridge at the site of the metopic suture. Finally, in our case there was a ridge in the situation in which the coronal suture was thought to be and no evidence of patency was obtainable by means of the roentgen ray.

It would be necessary to be content with the most indefinite ideas concerning the pathological conditions underlying the malformations of the head in the cases under consideration, were it not for the postmortem study of Rieping and the investigations on skulls showing similar malformations unassociated with deformities of the extremities. The evidence derived from the several sources of information makes it almost certain that in all the cases of our series there was present a synostosis of one or more of the cranial sutures. What, then, is the underlying cause of the defective growth of the skull in cases such as ours and what is the significance of the associated premature synostosis of the cranial sutures? The subject has been under active debate for the past seventy years.[53]

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[52] The superior maxilla and palatine bones are of membranous origin.

THEORIES CONCERNING THE PATHOGENESIS OF MALFORMATIONS OF THE SKULL CHARACTERIZED BY FETAL SYNOSTOSIS OF SUTURES

Within the limits of this paper it is impossible to give more than a brief outline of the theories of Virchow [55] and Thoma,[56] and to mention others. The greatest amount of study has been devoted to the commonest of the cranial malformations, scaphocephaly.

The effort has been made to explain scaphocephaly and the associated synostosis of the sagittal suture on the ground of the development of a single parietal bone extending bilaterally from a medially situated center (Minchin [57] (1856), Baer,[58] Fridolin [59] (1884), instead of the usual development of the two separate bones from two separate centers. The conception of a unituberal parietal bone originated in the interesting fact that in scaphocephaly, and also in acrocephaly, there is often a thickening in the region of the obliterated suture which resembles a center of ossification (Figs. 19, 20, 21 and 22). The unituberal theory, which is applicable only to a fraction of cases, has, however, been disproved and needs not be further considered. The disproof consisted in the discovery of remnants of the suture in skulls showing apparently a unituberal condition.[60]

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[53] 53. Backman[54] states that Hippocrates and Galen were familiar with the existence of malformations of the skull which they sought to bring into causative relationship with the condition of the sutures. General interest in the malformations of the skull dates from a publication by Virchow[55] in 1851 on malformations of the skull characterized by premature synotosis of the sutures.

[54] 54. Backman, G.: Ueber die Scaphocephalie, Anat. Hefte, Wiesb. **37**: 221, 1908.

[55] 55. Virchow, R.: Ueber den Cretinismus namentlich in Franken und über pathologische Schädelformen, Verhandl. d. phys. med. Gesellsch. in Würzb. **2**: 230, 1851. *In his:* Gesammelte Abhandlungen zur wissenschaftlichen Medizin, Frankf. a. M., 1856. Meidinger Sohn u. Comp., p. 1024.

[56] 56. Thoma, R.: (a) Synostosis suturae sagittalis cranii. Ein Beitrag zur Histomechanik des Skeletts und zur Lehre von dem interstitiellen Knochenwachstum, Virchow's Arch. f. path. Anat. **188**: 248, 1907. (b) Untersuchungen über das Schädelwachstum und seine Störungen. 1. Die Spannung der Schädelwand, Virchow's Arch. f. path. Anat. **206**: 201, 1911. (c) Anpassungslehre, Histomechanik und Histochemie, Virchow's Arch. f. path. Anat. **210**: 1, 1912. (d) Untersuchungen über das Schädelwachstum und seine Störungen. 2. Das fötale Wachstum, Virchow's Arch. f. path. Anat. **212**: 1, 1913. (e) Untersuchungen über das Schädelwachstum und seine Störungen. 3. Das postfötale Wachstum, Virchow's Arch. f. path. Anat. **219**: 80, 1915. (f) Untersuchungen über das Schädelwachstum und seine Störungen. 4. Hypostosen und Hyperostosen, Virchow's Arch. f. path. Anat. **223**: 129, 1917. (g) Untersuchungen über das Schädelwachstum seine Störungen. 5. Mechanische Wachstumsstörungen, Virchow's Arch. f. path. Anat. **224**: 78, 1917. (h) Untersuchungen über das Schädelwachstum und seine Störungen. 6. Rückblick und Schluss, Virchow's Arch. f. path. Anat. **225**: 97, 1918.

[57] 57. Minchin, H.: Contributions to Craniology, Dublin Q. J. M. Sc. **22**: 350, 1856

[58] 58. von Baer, K. E.: Die Macrocephalen im Boden der Krym und Oesterreichs, verglichen mit der Bildungs-Abweichung, welche Blumenbach Macrocephalus genannt hat, Mém. de l'Acad. imp. d. sc. de St. Petersb. **7**, serie 1860, **2**, No. 6. (Cited by Backman.)

[59] 59. Fridolin, J.: Studien über frühzeitige Schädeldifformitäten, Arch. f. path. Anat. **100**: 266, 1885.

In 1851 appeared Virchow's well known publication[55] on the deformities of the skull characterized by premature synostosis of the sutures. Although Virchow failed to distinguish between cretins and chondrodystrophiacs, and included the skulls of both in the material of his study, he set forth a classification of malformations of the skull on the basis of the relation of growth to premature synostosis of the cranial sutures which is in general acceptance today. Sömmering[61] (1839) and Hyrtl[62] (1846) had previously pointed out that an association appeared to exist between the closure of certain sutures and certain types of deformity of the skull. Virchow perceived a relationship beneath the association and defined it through

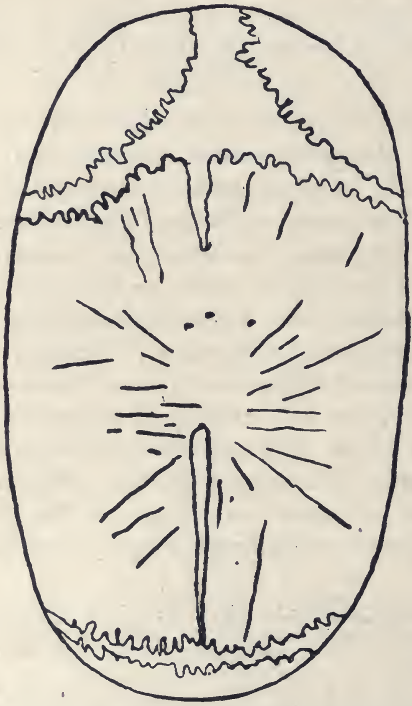

Fig. 20.—Scaphocephalic skull of fetus, reproduced from Wyman. Sagittal suture only partially obliterated. In line of obliterated suture is a thickened area of bone with radial striations resembling a center of ossification.

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[60] Wyman, J.: Observations on Crania, Museum of the Boston Society of Natural History, Boston, 1868, A. A. Kingman, p. 33. *Repr. from* Proc. Bost. Soc. Nat. His. **11**: 1868.

[61] Sömmering, S. T.: Vom Baue des menschlichen Körpers, Leipzig, 1839-1845, **2**: No. 139 und 142. [Cited by Backman.]

[62] Hyrtl, J.: Lehrbuch der Anatomie des Menschen, mit Rücksicht auf physiologische Begründung und praktische Anwendung, Prague, 1846, F. Ehrlich, p. 718.

the recognition of the principle that, when synostosis of two cranial bones occurs prematurely, normal growth is inhibited in a direction perpendicular to the obliterated line of suture, and compensatory growth takes place in other directions. Virchow held that the premature synostosis was the direct cause of the restriction of growth, and therefore, the primary cause of the cranial deformity itself. He seemed to have thought that an inflammatory process developed in the membranes of the brain, extended to the bones of the skull, destroyed their capacity for further marginal growth and caused them to become prematurely joined. The only evidence which Virchow found to substantiate the hypothesis of an inflammatory process was an eroded area, containing dilated blood vessels, in the middle part of the tabula of the occipital bone in an oxycephalic skull apparently belonging to an adult.

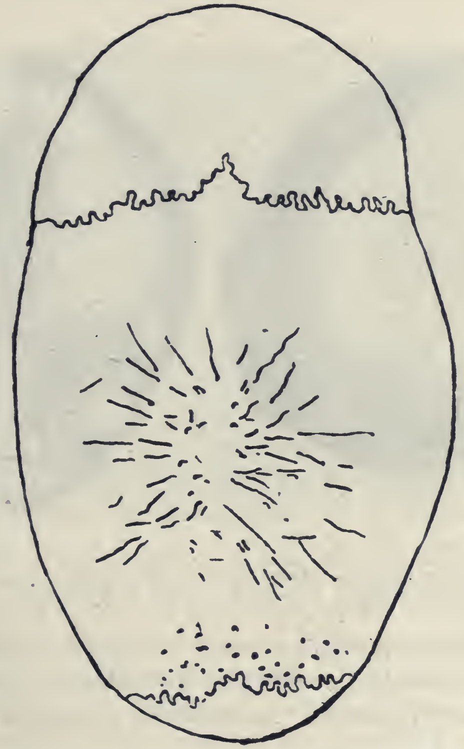

Fig. 21.—Scaphocephalic skull of 3-year-old child, reproduced from Wyman. Sagittal suture completely synostosed and not visible. In situation of sagittal suture is a thickened area of bone with radial striations resembling a center of ossification.

Virchow evidently thought that the injured skull actually obstructed the normal growth and development of the brain. He termed the condition resulting from the affection of the skull a "craniostenosis."

It would be difficult to overestimate the influence of Virchow's teachings in regard to the cranial deformities. It may be said without great exaggeration that his word has held thought bound. Though the great majority of investigators have dissented from the views expressed by him in regard to the exact mode of origin of the premature synostosis, few have challenged the basic principle involved of a restriction to growth due to a union of one bone with another before the normal time. Welcker[63] held that the pathologic process was primary in the bone. Indeed, with the exception of Broca,[64] Hirschberg[65] and a few of the earlier students of the problem, all exponents of the theory of premature synostosis have looked to pathologic conditions in the bone itself for the true explanation. Bonnet,[66] Oberwarth,[67] Berkhan,[68] Vorschütz[69] and Meltzer[70] ascribed the premature

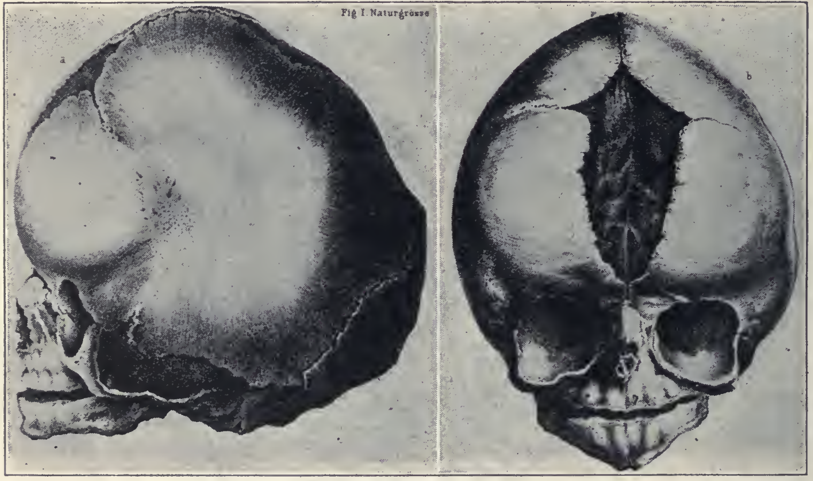

Fig. 22.—Photograph of oxycephalic skull of a new-born child, reproduced from Heschl. There is incomplete synostosis of coronal suture and in situation of synostosis an area of thickened bone with radial striations resembling a center of ossification.

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[63] Welcker, H.: Ueber zwei seltenere Difformitäten des menschlichen Schädels, Scaphocephalus und Trigonocephalus, und über die Frage nach dem zwischen Hirngröse und geistiger Begabung bestehenden Wechselverhältnisse, Halle, 1863. H. W. Schmidt, p. 19. *Reprinted from* Abhandl. d. naturf. Gesellsch. zu Halle, **7**. [Cited by Backman.]

[64] Broca, P. P.: Mémoires d'anthropologie, 3 v., Paris, 1871-1877, C. Reinwald & Cie, **2**: 1874. [Cited by Backman.]

[65] Hirschberg, J.: (a) Sehnervenleiden bei Schädelmissbildung, Centralbl. f. prakt. Augenh. **7**: 1, 1883. Hirschberg, J., and Grunmach, E.: (b) Ueber doppelseitiges Sehnervenleiden bei Turmschädel, Berl. klin. Wchnschr. **46**: 191, 1909.

[66] Bonnet, R.: Der Scaphocephalus synostoticus des Stettiner Webers, Eine Studie, Wiesbaden, 1904, J. F. Bergman.

[67] Oberwarth, E.: Ueber Turmschädel, Arch. f. Kinderh. **42**: 79, 1905.

[68] Berkhan, O.: Zwei Fälle von Skaphokephalie, Arch. f. Anthropol. **6**: 8, 1907.

[69] Vorschütz: Zur Frage des operativen Eingriffs bei Turricephalie, Deutsch. Ztschr. f. Chir., **99**: 386, 1909.

[70] Meltzer: Zur Pathogenese der Opticusatrophie und des sogenannten Turmschädels, Neurol. Centralbl. **27**: 562, 1908.

synostoses to fetal or postfetal rickets, and Marfan [71] to rickets in some cases. Hamy [72] referred the premature synostosis to an osteitis not improbably of syphilitic origin, and Mathouillet,[73] Fournier [20] and Frasset [74] definitely regarded it as a manifestation of hereditary syphilis.

Certain investigators have expressed doubt that the theory of premature synostosis was the true explanation of the malformation of the skull, or at least that it was applicable to all cases. [Wyman,[60] Huxley,[75] Giovanardi,[76] Backman,[54] Thoma.[56]] The explanation offered by Thoma is sufficiently distinctive to justify special consideration.

According to Thoma, the closure of the sutures in the normal skull is conditioned by the interaction of three factors: (1) the tension existing in the suture substance; (2) the ripeness of the suture substance; (3) movement in the suture substance. The basic principle of Thoma's mechanistic theory of development of the cranium is that when the tension in the membrane surrounding the brain, the brain capsule, rises above a certain point, designated by Thoma the critical point, the deposition of lime salts automatically sets in, and the membrane passes over into bone. This principle he applies to the mesenchymal substance (connective tissue) occupying the sutures of the skull. When, as the result of intracranial pressure, the tension in the suture substance rises above the critical point for the tissue of which the suture substance is representative, ossification occurs and the suture closes. Ossification of the suture material takes place more readily, however, that is, at a lower critical point if the suture material is ripe (Factor 2), and is allowed to remain free from movement (Factor 3). Had Thoma defined "ripeness" as ripeness, the reader would gain almost as clear an idea of his intended meaning as from the definition actually given. "Ripeness of the suture signifies a condition in which slight changes in the determining conditions lead to its ossification." [77] In whatever alterations "ripeness" may consist, the suture material actually becomes ripe according to Thoma, if its growth ceases or diminishes.[78] The third factor of movement in the suture material also requires explanation. Thoma holds that movements are communicated to the suture material of certain sutures, for example, the sagittal, coronal and lambdoidal, as the result of changes in intracranial pressure caused by the variation in arterial blood pressure with each cardiac cycle, and in the venous pressure with each respiratory cycle, and prevent closure. When the sutures do finally close, it is only because of the decline in the activity of circulatory and respiratory mechanisms with advancing age.

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[71] Marfan: Rachitisme. *In* Traité de médicine et de therapeutique (Brouardel), Paris **3**: 1897. [Cited by Backman.]

[72] Hamy, E. T.: Étude sur la genèse de la scaphocéphalie, Bull. Soc. d'anthrop de Par. **9**: 836, 1876. [Cited by Backman.]

[73] Mathouillet, P. A.: Étude sur la scaphocéphalie, Paris, 1880, No. 142, p. 142. [Cited by Backman.]

[74] Frassetto, F.: Appunti sulla scafocefalia patologica, Atti. d. Soc. rom. di antrop. **11**: 195, 1905. [Citd by Backman.]

[75] Huxley, T. H.: On Two Widely Contrasted Forms of the Human Cranium, J. Anat. & Physiol. **1**: 60, 1867. Abstr. in Anthrop. Rev. **4**: 404, 1866.

[76] Giovanardi: Di un cranio scafocefalo ed ultra dolicocefalo. Atti della società dei Naturalisti di Modena, Ser. **3**, 1894, **13**: 41. [Cietd by Backman.]

[77] Thoma,[56]g page 111.

[78] If, for example, growth at the sagittal suture has almost ceased, ossification of the suture substance will take place under a lower tension than if growth in the suture material were actively in progress.

By means of a juggling of the three factors mentioned—at least so it seems to us—Thoma is able to explain all variations in the normal time of closure of the sutures from the closure of the metopic which takes place in the first year of life [79] to the closure of the coronal and lambdoidal sutures which take place usually during the fourth and fifth decades. By summoning a fourth factor, external pressure, he is enabled to explain all *abnormal* closures of sutures during fetal life. We are now in a position to understand Thoma's explanation of the closure of sutures prematurely in fetal life.

Premature synostosis of the sutures occurring during fetal life in scaphocephaly, acrocephaly, oxycephaly, trigonocephaly and plagiocephaly are brought about through the agency of external pressure (the new factor, Factor 4). The external pressure so alters physical and chemical conditions (tension, movement and ripeness) in the suture material that ossification is induced prematurely. The compressing mechanism is the uterine musculature. In scaphocephaly the head of the fetus is gripped by the uterus from side to side, and the margins of the parietal bones brought together and held in contact. Movement in the suture material as the result of circulatory and respiratory changes can no longer be operative. The suture material released from the tension caused by the continued pressure of the growing brain ceases to grow; therefore it becomes ripe. Although the tension in the suture substance is reduced, ossification with resulting premature synostosis takes place. It is necessary to suppose that, although the uterine wall exerts strong pressure on the sides of the head of the fetus, i. e., in the short diameter, it exerts little or no pressure on the ends, i. e., in the long diameter. Accordingly, prevented from growing in a transverse direction, the skull undergoes compensatory growth in a sagittal direction against those parts of the uterine wall in a less contracted or noncontracted state. In the case of acrocephaly or oxycephaly the premature synostosis comes about in a somewhat different way. The uterus is now conceived as gripping the head in its longest diameter, from before backwards, but as leaving the lateral portions free. The tension in either the coronal or lambdoidal sutures or in both rises; the critical point is exceeded, and ossification occurs. The factors of ripeness and movement apparently do not enter into the ossification of these sutures. In plagiocephaly (asymmetrical skull) not due to tumor or defective development of the brain, pressure is exerted by the uterine wall upon the skull diagonally, leading to an asymmetrical synostosis.

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[79] The metopic suture normally closes between the ninth and twelfth months according to Welcker.[68a]

It is, of course, difficult to imagine how the uterine wall could compress the head of the fetus, as Thoma supposes, since the pressure exerted by the uterus under normal conditions is a fluid pressure. Accordingly Thoma is compelled to assume that oligohydramnios is present. Moreover, on account of the peculiar ridge formation at the sagittal suture a not infrequent accompaniment of scaphocephaly, Thoma is forced to suppose that the period at which the uterus exerts its pressure on the skull of the fetus is, comparatively speaking, late, when the margins of the flat bones are in contact with each other.[80]

Finally, it is necessary to call attention to a theory brought forward as early as 1875 by Morselli[81] and recently *de novo* by Rieping.[15] These two writers expressed the view that the premature synostosis was a physiologic process consummated prematurely because the ossification centers of the bones involved happened to be placed in abnormal proximity to each other. Morselli wrote: "If the two primary ossification points (of the parietal bones) approached each other and came to lie in the closest proximity to the *regio mediana parietalis,* this would be a very plain, simple physiological explanation of scaphocephaly in accord with the principles of histological anatomy.[82] Rieping expressed himself as follows: "The malformation (oxycephaly) is determined by variations in the germ plasm, manifested by a dislocation of the primary ossification centers of frontal and parietal bones toward the coronal suture with the result of a premature synostosis."[83]

Although the theories advanced by Virchow and his school and by Thoma appear to be widely different, in the basic principles involved they are strikingly similar. Both held that the germ plasm was normal and the fetus in all its stages of development was normal until ossification of the cranium was far advanced. Both held that the fetal cranium, including the parts immediately concerned in the premature synostosis and defective development was normal and possessed of the normal potentialities of growth and development until suddenly deprived of them (Virchow) or of the power further to exercise them (Thoma) as the result of an accident (inflammation [Virchow], uterine pressure [Thoma]). Both held that the pathologic process at the basis of the malformation had to do with ossification.

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[80] Thoma reasons as follows: If the pressure of the uterus on the sides of the head of the fetus occurred before the margins of the parietal bones had met, the sagittal suture in cross section of the skull would lie at the summit of a rounded arch. In scaphocephaly, however, the sagittal suture, if pushed upwards at all, forms the summit of a ridge (Fig. 23). Pressure must, therefore, have been exerted after the margins of the bones were in contact.

[81] Morselli, E.: (a) Sullo scafocefalismo, Arch. per l'antrop., Firenze **5**: 22, 1875. [Cited by Backman.] (b) Sur la scaphocéphalie, Bull. Soc. d'anthrop de Par. **10**: 443, 1875. [Cited by Backman.]

[82] Quoted by Backman,[54] pp. 234 and 235.

[83] Rieping,[15] p. 44.

So far as we are aware, all students of the problem, no matter what their particular views, have regarded the malformation of the skull as due to a disturbance in the process of ossification.

The theories of Virchow and his followers and of Thoma require only brief discussion. It is impossible to think that the malformation of the skull was the result of inflammation localized, so to speak, in certain of its crevices. What inflammatory process would select with such specificity a single suture line or the middle part of a suture line, or the corresponding parts of a single suture line, on opposite sides of the skull, or the same combinations of sutures, and be of sufficient severity to destroy the capacity of the cranial bones for further marginal growth and cause them to become locked together and yet disappear without leaving a trace of its existence in the synostosed bones themselves, or in the membranes beneath? Why are such inflammatory processes not found in the lines of sutures in postfetal life? There has never been produced one particle of evidence to show that premature synostosis of the cranial sutures was caused by inflammation. The theory that the malformation of the skull is the result of inflammation has, therefore, not one single fact to support it.

The reasons that the malformations of the skull cannot be caused by syphilis have already been given. The reasons that they cannot depend on rickets are only too apparent. The malformations of the skull are fully developed at birth. We have no good reason for admitting the existence of fetal rickets. Even in postfetal life there is no ground for thinking that rickets gives rise to premature synostosis of the cranial sutures. The subjects of the malformations with one or two exceptions, were apparently free from rickets.

It is also impossible to accept Thoma's theory that premature synostosis and the associated deformity of the skull are the results of pressure by the uterus on the fetus. The evidences of pressure upon the fetal skull cited by Thoma in scaphocephaly, consisting of the keel shaped ridge, the thickening of the joined parietal bones, their peculiar bend with concavity outward (Fig. 23), are not in the least convincing. How is it possible that in scaphocephaly the uterus can press together the sides of the head (the shortest diameter) and leave the ends (the longest diameter) free; and in acrocephaly that it compresses the head in the long diameter and leaves the sides free;

and that in trigonocephaly it presses together the anterior part of the head and leaves the middle and posterior parts free, and that in plagiocephaly it compresses the head in one diagonal and leaves it free to grow in the other? If sufficient amniotic fluid is present, the pressure exerted by the uterus must be fluid pressure and such gymnastic feats are impossible. If there is a condition of oligohydramnios, all parts of the fetus, not alone of the head but also of the body, should be affected. Such a question, however, as the one raised by Thoma's theory must not be decided on theoretical considerations when facts are available. Is synostosis of the cranial bones one of the recognized pathological findings in the fetus when oligohydramnios was present? We cannot find it mentioned among them. Is there a history of oligohydramnios in all cases of deformity of the skull such as we are considering? In our series of twenty-five cases a history of oligohydramnios was not given once. In three of the cases there was a history of polyhydramnios (Cases 6, 8 and 12). In our case the history stated that the amniotic fluid seemed to be abundant. Fournier[84] writes of his case: "When this woman went into labor, she discharged a quantity of fluid so abundant that it overflowed from the bed and inundated the room." One single case such as that of Fournier is enough to upset Thoma's theory.

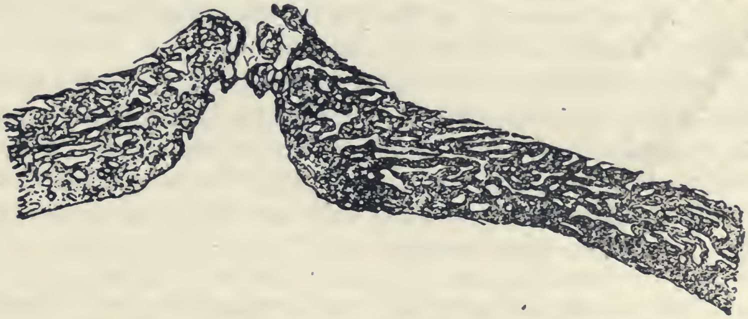

Fig. 23.—Cross-section through the synostosed sagittal suture of the scaphocephalic skull of a new-born child. The section is taken in the frontal plane at a point where union of the parietal bones is only partial. Note that the edges of the bone close to the point of union are bent upward so that externally a ridge is formed. Note also that there is a thickening of the bone on the inner side of the skull. (Reproduced from Thoma.)

It is difficult to accept some of Thoma's conclusions in explanation of phenomena connected with the growth and development of the *normal* skull. We cannot be persuaded, for example, that movements communicated to the suture substance as the indirect result of circulatory or respiratory activity influence the closure of the sutures or that an increase in the tension to which the suture substance is subjected, if sufficiently great, causes the suture to become prematurely synostosed. In congenital internal hydrocephalus, due to an obstruction of the basal foramina or the aqueduct of Sylvius, and in acquired hydrocephalus, the result of a meningococcus meningitis, premature synostosis of the cranial sutures not only does not occur but the margins of the flat bones of the vault, though presumably still growing, actually recede from each other until the suture lines become represented by broad membranous lanes. When brain tumor develops in a child with a normal skull, the greatly increased intracranial pressure drives the cranial bones apart instead of causing them suddenly to seal together. It would be a strange provision of nature if the sudden urgent requirement for increased intracranial capacity were to be met by the withdrawal of the only means by which it could be rapidly furnished. We believe that some of Thoma's theories, when applied in explanation of the malformations of the skull of the group now under consideration, undergo a *reductio ad absurdum.*

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[84] Fournier,[20] p. 244.

Of all the students of the cranial deformities, Morselli and Rieping, in our opinion, have approached nearest to the most probable explanation. Rieping, in particular, entertained conceptions which, if carried to their logical conclusion, must have forced the assumption that the defective development of the bony skull was merely the expression of a defect in the blastemal cranium.

FROM THE MALDEVELOPMENT OF THE EXTREMITIES, IT IS POSSIBLE TO INFER THAT THE CRANIAL DEFECT WAS PREEXISTENT IN THE BLASTEMAL CRANIUM

If due to defects inherent in the germ plasm, the deformities of head and extremities originated synchronously, and must have emerged together out of the obscurity of the beginnings of embryonic existence. But in the event that they were acquired together as the result of some injurious influence or combination of influences after embryonic life had once been established, it is possible that the defective development of the extremities preceded that of the head. If, however, the injury to the extremities was received not later than the eighth week of embryonic life, as we believe it necessary to think if an injury was ever received at all, it is altogether improbable that the injury to the skull was delayed until ossification in the cranial vault had progressed so far that the edges of the flat bones were almost in contact with each other. From the knowledge that the deformities of the extremities almost certainly were in existence in the blastemal period, it becomes altogether likely, therefore, that the defective development of the skull was preexistent in the blastemal cranium. We believe that the facts brought out by the study of the malformations of the extremities indicate that the defective development of the skull must be thought of as having been present in the blastemal cranium and that all theories based on the assumption that ossification was primarily at fault must be abandoned.

THE GENERAL CONSIDERATION OF THE PROCESS INVOLVED IN THE OSSIFICATION OF A SUTURE LIKEWISE INDICATES THAT THE CRANIAL DEFECT MUST HAVE BEEN PREEXISTENT IN THE BLASTEMAL CRANIUM

Ossification of membrane is to be thought of not as a formation of a new tissue but as a transformation of an existing tissue with the addition of large quantities of inorganic matter derived from the blood. Hence, the defectively developed portions of the bony cranial vault are to be regarded as the defective portions of the blastemal vault transformed from a membranous to an osseous state.

If, similarly, we inquire into the relationship of the deformities in the bony skeleton of the hands and feet to the deformities which we know must have existed in the blastemal skeleton, we come to the same conclusions. Obviously the deformities in the bony skeleton of the hands and feet can be thought of only as deformities of the blastemal skeleton transformed through the intermediary of cartilage from a state of membrane to one of bone.

If now accidental causes such as rickets, inflammation, external pressure, etc., are excluded as the controlling factors, as we believe they must be, the consideration of the process involved in the closure of a suture leads to the conclusion that the cranial defect must have preexisted in the blastema. So long as the cranial bones are separated by mesenchymal tissue through the continued transformation of which into bone they grow, they cannot meet to become synostosed. Obviously, synostosis can occur only after the separating zones of mesenchymal tissue have been completely transformed and have disappeared. Premature synostosis signifies, therefore, a disturbance not in the bone but in the growth or development of the mesenchymal matrix in which the bone was laid.

Thus, the study of the malformations of the hands and feet and general consideration of the process involved in the synostosis of the cranial sutures alike indicate that the malformation of the skull, in a potential sense, at least, was already in existence in the blastemal cranium. Either the defect must have arisen in the mesenchymal capsule or its precursors or have been present in the germ plasm itself.

THE PROBABLE MEANING OF SYNOSTOSIS OF THE BONES OF THE CRANIAL VAULT IN FETAL LIFE

From the situations of the lesions along the lines of suture in the malformed skulls under consideration, it is possible to infer that the defective portions of the blastemal vault could not have corresponded in their arrangement to the pattern later established in the bony vault through the formation of the cranial bones, but that they must have lain in places destined under normal conditions to include the sites of sutures; i. e., the defective portions appear not to have corresponded to the individual primordia [85] of cranial bones.

The general principle involved in premature synostosis must be as follows: The margins of two islands of bone extending toward each other in the blastemal matrix meet prematurely and unite for the reason that the mesenchymal tissue between them does not keep them apart. Under normal conditions the mesenchymal tissue intervening between the margins of two bones keeps the bones apart, or at least delays their progress toward each other by continuous interstitial growth. It is easy to understand that, if the mesenchymal tissue did not grow at all, or grew at a diminished rate, the margins of the bones would prematurely come in contact with each other. If, now, the essential element in the defect in the blastemal cranial vault consisted in the loss of, or diminution in, the property of normal growth, premature synostosis might be conceived of as occurring for the reason that growth of the blastema ceased prematurely. It would, then, be necessary to think that all the steps requiring years for completion in the closure of a suture in the normal cranium followed close on each other in the defectively developed cranium of the fetus, and were condensed, so to speak, into a period of a few days or weeks.

There is reason to think, however, that synostosis of the cranial bones reaching completion in fetal life is more than a simple acceleration of the normal process. Just as the structures which comprise the joint, the articular cartilages, ligaments, etc., resist ossification indefinitely, so, as is well known, the residuum of the blastemal membrane that comes finally to occupy the lines of suture between the cranial bones, namely, the suture substance, resists ossification in some of the suture lines for years after growth has ceased. It is possible that in the malformed crania blastemal tissue, perhaps, in particular the blastema corresponding to the ultimate suture substance, possessing very probably special properties of growth and resistance to ossification, was defectively developed or actually absent? Such a possibility is suggested when the analysis of the development of the pathological synostoses in the deformed extremities is attempted.

If inquiry is made into the cause of the end to end synostosis between the phalanges, to take a specific example, the first and second phalanges of the left great toe in our case (Fig. 9), the explanation in principle appears to be as follows: From the fact that the bones of the extremities are preformed in cartilage it seems necessary to suppose that at an early period of embryonic life the cartilaginous first phalanx and the cartilaginous second phalanx were in contact with each other instead of being separated as under normal conditions by mesenchymal elements representing the structures forming the joint. As ossification progressed in the two cartilaginous phalanges in question and the margins of the growing cores of bone moved toward each other, they inevitably met and synostosis took place for the reason that the cartilaginous matrices predestined to become bone were in contact, that is, because no nonosteogenic tissue existed between the two cartilaginous phalanges that could keep them separate. If, now, inquiry is made into the cause of the side to side synostosis accompanied by bridge formation between the metacarpal bones of the right great and second toes of our case (Fig. 9), the explanation must be the same as that already given. It is necessary to think that in fetal life the cartilaginous metacarpal bones representing the two osseous metacarpal bones were connected by a cartilaginous bridge. As the margins of the central cores of bone approached across the bridge, they met and fused because cartilaginous matrix predestined to become bone was continuous with cartilaginous matrix predestined to become bone; in other words, they met and fused because the nonosteogenic tissue normally interposed between them was absent.

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[85] By primordium of a cranial bone is meant that portion of the blastemal cranium which ultimately becomes transformed into a cranial bone.

The study of the pathologic synostoses of the extremities suggests, therefore, that in the blastemal cranial vault blastemal elements were actually lacking or in some way defectively constituted with the result that when ossification began, the primordium of one cranial bone was in immediate contact or continuous with the primordium of another. Naturally, it is not possible to arrive at positive conclusions concerning the causes which led to the pathologic closure of the sutures in fetal life. It seems to us necessary to infer, however, that blastema was lacking, or defectively constituted, in the sense that it never grew or grew imperfectly or did not develop the qualities enabling it to resist ossification.

In regard to the *ultimate* nature of the defect in the blastemal cranium, there is nothing to say. In all congenital malformations the ultimate nature of the defect is enveloped in impenetrable obscurity. In congenital esophageal stenosis, for example, we know that a portion of the alimentary tube remains in a rudimentary state, and in congenital pulmonary stenosis that the infundibulum or the valvular orifice does not develop. We cannot even surmise what substance or inherent force was lacking in the tissues themselves or what inhibiting influence was exerted which prevented natural conditions from being realized. Until the forces and principles which determine normal growth and the assumption of normal form are understood, it is idle even to speculate concerning the abnormal.

CERTAIN POINTS OF SIMILARITY IN THE MALFORMATIONS OF HEAD AND EXTREMITIES

It is impossible not to be impressed by certain similarities between the malformations of the extremities and those of the head in our cases.

1. The malformations of head and extremities are both regional defects involving soft tissues as well as bone.

2. In both skull and the skeleton of the hands and feet the striking lesion is synostosis, pathologic in the case of the extremities, because it ought never to have occurred, pathologic in the case of the skull, because of its occurrence before its time.

3. In both skull and extremities those parts developed last (the vault of the skull, the ends of the extremities) appear to be most affected.

4. In the distribution of the deformities in the skull and extremities there is exhibited a common tendency toward symmetry.

If the skulls in the twenty-five cases were available for study, we believe that we should be able to find counterparts for various types of deformity in the bones of the extremities, such as union of two bones for only a part of their length, union for their entire length, union partial or complete with essentially no reduction in the width of the bones involved, union partial or complete with moderate or marked reduction in the width of the affected bones, defects of very limited extent associated with extremely slight malformations in the shape of the skull, defects so widespread as to include most parts of the osseous cranium. As a matter of fact, we already know of the existence of skulls exhibiting types of malformation similar to types of malformation present in the hands and feet. The scaphocephalic skull of a 3-year-old child described by Wyman[60] (Fig. 21) shows a synostosis of the two parietal bones so complete that the two bones appear as one. A fetal scaphocephalic skull described by the same author (Fig. 20) is characterized by union of the two parietal bones only in their middle part. The oxycephalic skull of a new-born child described by Heschl[85] *a* (Fig. 22) is marked by an almost complete fusion of frontal and parietal bones. The acrocephalic skull of a new-born child described by Zuckerhandl[86] (Fig. 19) displays central union

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85*a*. Heschl: Fötale und prämature Obliterationen der Schädelnähte nach Fällen der Grazer Sammlung, Vrtljschr. f. d. prakt. Heilk., Prag. **123**: 1, 1874.

86. Zuckerkandl, E.: Ueber oxycephale und acrocephale Cranien, Mitth. d. anthrop Gesellsch. in Wien **4**: 153, 1874.

of frontal and parietal bones of slight extent with gaping sutures on either side comparable, perhaps, to union with bridge formation seen in the extremities. The greatly malformed acrocephalic skull of Fridolin[59] (Fig. 24) is an example of multiple synostosis.

THE BLASTEMAL CRANIUM NOT TO BE REGARDED AS A SHEET OF INDIFFERENT CONNECTIVE TISSUE

According to our conception of the origin of the malformations of the bony cranium, it is difficult to regard the blastemal cranium as a sheet of indifferent connective tissue, having no individuality and chancing to undergo ossification merely because it happened to be so situated as to become subject to the peculiar pressure influences of the growing brain. It seems to us reasonable to think of the blastemal cranium as possessed of the same specialization as the blastema of the hand and foot plates or the blastemal precursors of all other parts of the skeleton. It seems probable that, as growth proceeds, there develops in the blastemal cranium a blastemal skeleton corresponding to the future osseous skeleton, exactly as a blastemal skeleton corresponding to the future osseous skeleton is formed in the hand and foot plates. In the extremities the various bones are separate from each other. Their blastemal representatives are distinct and permit of recognition, even though the distinction from the environment con-

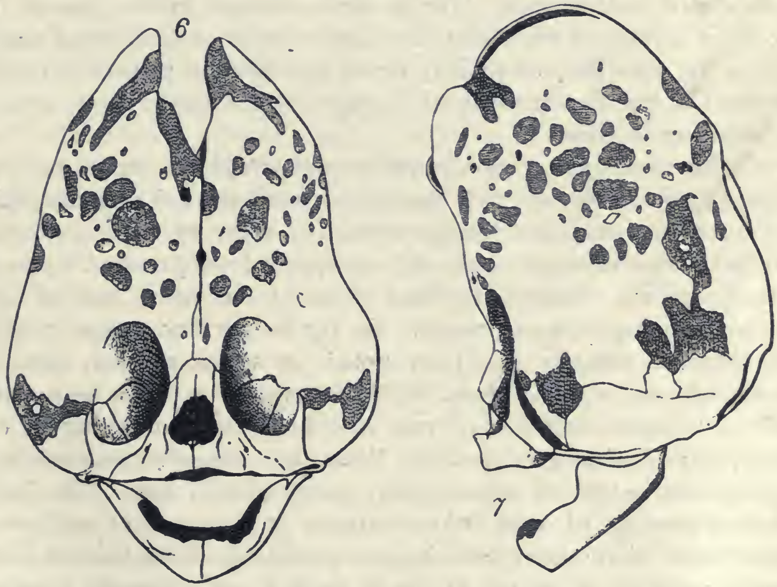

Fig. 24.—Acrobrachycephalic skull of a new-born child, front and lateral views, reproduced from Fridolin. Coronal suture synostosed, except in its upper part. Lambdoidal suture synostosed except perhaps in its lower part. Extreme degree of convolutional atrophy.

sists solely in an increased density. In the cranial vault conditions are totally different. The skeleton there forms a continuous surface and the recognition of a blastemal skeleton, differentiated merely by a condensation of mesenchyme, is rendered extremely difficult. As we have already indicated, the development of the membranous cranium has never been adequately studied and still remains in obscurity.

EVIDENCE OF INTRACRANIAL PRESSURE IN EXCESS OF THE NORMAL

We now turn to the consideration of the intracranial pressure. There is evidence that the intracranial pressure has exceeded the normal in the great majority of subjects of the malformations of the skull under consideration. The evidence consists in the presence on the inner surface of the skull of areas of atrophy as determined during life by the roentgen ray and by direct examination at necropsy, and, further, in the development of changes in the eye-grounds and of disturbances in vision.

So far as we are aware, convolutional atrophy is an almost constant accompaniment of well marked acrocephaly and scaphocephaly. We have seen only one roentgenogram in either of those conditions in which convolutional atrophy did not appear to be present; it may be a most striking feature. In those cases of our series studied with the roentgen ray it was present. So far as our knowledge extends, convolutional atrophy has been noted in all necropsied cases of oxycephaly and scaphocephaly, in which search for it has been made, with the single exception of one case happening to belong to our series, that of Rieping (Case 20). Wheaton commented on its striking development in the two cases studied postmortem by him. The almost constant presence of convolutional atrophy in the group of malformed skulls under discussion proves beyond reasonable doubt that an intracranial pressure in excess of the normal is an extremely common associated condition.

The alterations in the eye-grounds and the visual disturbances, present probably in a majority of cases, can be explained only on the ground of an increased intracranial pressure.

THE CAUSE OF THE INCREASED INTRACRANIAL PRESSURE

There are three possible causes for the increased intracranial pressure: Either the cranium is abnormal and offers an increased resistance to normal growth of the brain or the intracranial contents are abnormal and generate an increased intracranial pressure or both conditions are present. We shall first consider the possibility that the increased intracranial pressure is the result of a craniostenosis, the cranial contents being normal.

According to the views already expressed, certain parts of the cranium are defectively developed. It is presumable that these parts do not furnish their normal quota of surface per unit of time in response to the pressure demands of the growing brain. If the growth of the brain continues uninterrupted, it is necessary that portions of the cranium, capable of response, contribute more than their normal quota of surface per unit of time. To make such portions grow faster than at their normal rate or possibly in excess of their normal limits increased pressure is required. Intracranial pressure, therefore, rises.

The explanation for the development of the increased intracranial pressure just given is hypothetical. Provided, however, an internal hydrocephalus is not the cause, in principle it must be assumed to be correct, whether the theory of origin for the defective development of the cranium offered by us or the theories of Virchow, Morselli or Thoma are accepted. It is probably tenable, if (1) the expansive growth of the cranium varies directly with the intracranial pressure and (2) the brain substance will generate an intracranial pressure in excess of the normal in order to fulfill its inherent demand for growth.

Observations made in the study of internal hydrocephalus and microcephalus make it appear that the expansive growth of the cranium bears a relationship to intracranial pressure. So far as we know, the cranium never undergoes expansive growth independently of the growth of its contents. We can supply no direct evidence, however, to show that the brain can create an intracranial pressure above normal limits except the very inconclusive observations of Wheaton and those of Schumacher.[87] Wheaton noted at necropsy in his two cases that the brain seemed to be under increased tension from the manner in which it bulged through the dura mater as soon as the latter was incised. At necropsy in a subject of oxycephaly showing during life indubitable evidences of an increased intracranial pressure, Schumacher failed to find evidences of a hydrocephalus. The conclusion follows that the brain tissue had generated the increased pressure in order to accomplish its growth against an increased resistance. There is little doubt that in common with other tissues the brain has the power to create a pressure in excess of the normal when its growth is obstructed, though it undoubtedly possesses this power to a much more limited extent than the less highly specialized tissues.

The second of the three possible causes for the increased intracranial pressure is "internal hydrocephalus." That internal hydrocephalus gives rise to increased intracranial pressure is too well known to require discussion. The question to be considered is whether in the malformed skulls an internal hydrocephalus is present. As just pointed out, in Wheaton's two cases an internal hydrocephalus was not present. Strongly suggestive of the nonexistence of hydrocephalus in the series of cases collected by us is the fact that in those subjects measured the circumference of the head was less than the normal (Table 2). In Rieping's case, however, a small internal hydrocephalus was discovered at necropsy, even though the circumference of the head was under the normal figure. In a number of the subjects of oxycephaly and scaphocephaly unaccompanied by malformation of the extremities, the existence of internal hydrocephalus has been proven at necropsy. In the case of a scaphocephalic patient under our observation an internal hydrocephalus apparently of considerable proportions was demonstrated during life (Case 30). On the other hand, uncomplicated cases of scaphocephaly have been reported in which no internal hydrocephalus was demonstrable at necropsy.

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[87] Schumacher, E. D.: Entlastungstrepanation oder Balkenstich bei Turmschädel mit Hirndruckerscheinungen? München. med. Wchnschr. **59**: 2282, 1912.

The data at hand are altogether too insufficient to permit of positive conclusions. It appears, however, that in some cases of well marked acrocephaly and scaphocephaly no internal hydrocephalus is present. It is certain that in other cases an internal hydrocephalus of considerable proportions is present. If hydrocephalus was present in our series, it did not reach well marked degrees of development in any of those cases in which measurements of the skull were taken and probably in none of the cases.

The reason that internal hydrocephalus should be associated with synostotic malformations of the skull, except as a chance occurrence, is not clear. The possibility that the internal hydrocephalus is merely the result of a disturbed relation between the formation and absorption of the cerebrospinal fluid secondary to the craniostenosis apparently cannot be entertained. According to the explanation offered by Rieping, the internal hydrocephalus is the result of an interference in the circulation of the cerebrospinal fluid, due to a narrowing of the passageways because of the cramped condition of the brain. Another possible explanation is that the membranes themselves are defectively developed. The membranes surrounding the brain are most closely related to the skull in origin and development. It would be easy to understand that the membranes might share in the defect. We cannot offer any explanation for the coexistence of internal hydrocephalus and the cranial malformation that is satisfactory.

We are inclined to believe that the defective development of the cranium can be the sole cause of an increased intracranial pressure. In those cases, however, in which hydrocephalus is present, it cannot be denied that it may be a factor. In some cases it is probably the chief factor concerned.

We are under the impression that the intracranial pressure in the great majority of cases of acrocephaly and scaphocephaly does not reach extreme degrees of development. We have seen a case of acrocephaly and one of scaphocephaly complicated by small meningoceles. In the one the meningocele appeared only when the child cried; in the other it was constantly present but was not under tension.

ELEMENTS IN THE CRANIAL MALFORMATION APPARENTLY ATTRIBUTABLE TO THE INCREASED INTRACRANIAL PRESSURE

According to our conceptions, even if there had been no force in excess of the normal within the cranium, it still would be necessary to suppose that the skull, as a whole, would not have been normally formed on account of the defective development of certain of its parts. Under the influence of an increased intracranial pressure it would seem that the disproportionate development must have been greatly augmented. Apparently parts of the cranium capable of response to the stimulus were forced to grow beyond the normal limits in whatever directions growth could take place most easily; no part of the skull, however remote from the intracranial cavity, entirely escaped the deforming effects and the relations of all parts of the skull to each other, especially those forming the cerebral cranium, were profoundly disturbed.

The malformation of the cranium is exceedingly complicated. We cannot attempt to analyze it but merely mention some of the striking elements for which the increased intracranial pressure appears to be responsible. The excessive height and breadth of the cranial vault, the low level of the lamina cribrosa and the great depth of the middle and posterior fossae must be regarded as the effects of an increased pressure. It is probable that the flattening of the base, i. e., the reduction in the acuity of the sphenoidal angle, when present, is an expression of the effect of the increased pressure, as Bertolotti and Boidi Trotti considered. The malformation of the orbit is attributable, at least in part, to the increased pressure. The necropsy study in the case of Rieping and similar studies in cases of oxycephaly uncomplicated by malformation of the extremities have shown that the depth of the orbit is reduced. We have seen a similar reduction in the depth of the orbit in the artificially deformed skull of a Flathead Indian. The eyeball is more prominent than normal merely because the orbital cavity is more shallow than normal. The slant of the palpebral aperture and the external rotation of the eyeball about its anteroposterior axis are to be explained in all probability by an alteration in the lateral contour of the orbital cavity of such nature that its outer part has come to occupy a lower level than its inner and the transverse diameter has acquired a direction from within outward and downward. In the normal infant, the transverse axis of the orbit is directed only slightly downward. In the greatly malformed acrocephalic skull of a new-born child described by Zuckerkandl (the skull shown in Fig. 19 but in anteroposterior view) the transverse diameter of the orbit is directed outward and considerably downward and in the still more malformed skull of Fridolin the transverse diameter of the orbit (Fig. 24) has become almost vertical. The external strabismus which developed gradually in our case and was a feature in a number of other cases is probably also to be explained on the ground of the malformation of the orbital cavity. The great breadth of some of the lines of suture and the large size of the anterior or posterior fontanels are probably to be interpreted as in ordinary internal hydrocephalus on the principle that growth in the membrane separating the bones has occurred under the stimulus of the increased intracranial pressure with such rapidity that the margins remain widely separated. The reason that the posterior fontanel was larger than the anterior fontanel in our case and the case of Rieping probably was that the expansive growth occurred there more easily than in the region of the anterior fontanel.

We cannot explain the presence of the large serrations along the edges of bone bordering on gaping fontanels and sutures, noted in the case of Wheaton and in other cases, and the presence of the wormian bones in the large fontanels and sutures. We are able to point out merely that wormian bones and marked irregularities in the edges of the bones are frequently met with in the subjects of ordinary internal hydrocephalus with large fontanels and widely patent sutures. They have no specific significance in the malformations under discussion.

THE SIGNIFICANCE OF THE PRESENCE OF A MASS OF BONE RESEMBLING A TUBEROSITY AT THE POINT OF SYNOSTOSIS AND THE APPARENT ABSENCE OF THE TUBEROSITIES FROM THEIR NORMAL SITUATIONS

In a study of 116 cases of scaphocephaly, the majority taken from the literature, Backman reported that the parietal eminences were absent in sixty-seven. In the remaining forty-nine cases they were present. In thirty of the forty-nine cases the eminences were rather poorly developed but in the remaining nineteen they were well developed. Backman's observation that in those cases in which the scaphocephalic deformity was extremely marked the parietal eminences were in general wanting may have special significance.

Why should the parietal and frontal eminences ever appear to be absent in malformations of the skull accompanied by intra-uterine synostosis of the sagittal, coronal or metopic sutures, and a circular thick mass of bone with peripheral radiations, bearing some resemblance to a parietal or frontal eminence, mark their junction (Figs. 19, 20, 21, 22). We cannot answer the question, but suggest two hypotheses.

The first hypothesis is that the circular mass of bone resembling a center of ossification is not actually a center but represents a defective area in the blastemal vault. It is conceivable that the defect in the blastema might manifest itself in the bony vault by an increased thickness as well as by a diminished growth in surface dimensions. *A priori* various irregularities in ossification in the region corresponding to the blastemal defect might be expected. The second hypothesis is that the blastema separating the centers of ossification or, perhaps, including one of them, was lacking or did not develop normally, with the result that the two centers merged or only one developed. This hypothesis falls into agreement with the observation that in marked synostotic malformations of the skull the tuberosities often appear to be absent and would make comprehensible their proximity to each other when present. It differs fundamentally from the explanation offered for the same phenomenon by Morselli and Rieping. Rieping assumed that the conditions and processes in operation in the oxycephalic cranium were normal, except that the centers of ossification, through an oversight of nature, happened to be placed in abnormal proximity to each other. He seems to have thought that as soon as the margins of the bones of the vault met, synostosis occurred and consequently that the time of occurrence of synostosis of one cranial bone with another was determined merely by the distances that separated their respective centers of ossification and to have been oblivious to the fact that along certain sutures the edges of the cranial bones lie in virtual contact with each other for twenty, thirty or even forty years before synostosis takes place. No matter how close to each other in the membranous cranium the centers of ossification happen to be placed, it would by no means follow that synostosis would occur prematurely and the centers become one.

RIDGE FORMATION AT THE SITE OF THE SYNOSTOSED SUTURE

The study of the hands and feet furnishes evidence that the union of the synostosed bones in many places was partial and in a mechanical sense must have been imperfect. It seems probable that the union of the synostosed bones of the cranial vault, particularly at the beginning of the process, may, in some instances, have been imperfect

(Fig. 23). If the line of union of two cranial bones were weaker than the substance of the bone on either side, yielding outward to the increased intracranial pressure in the course of growth would be apt to occur, if it occurred anywhere, along the line of union. The thickening of the bones on the inner surface of the skull near the synostosed suture appears to be analogous to the thickening of the periosteum, developing on the side of the rachitic bone away from the direction of yielding. The curvature of the edges of the bones close to the synostosed suture of such nature that their external surfaces (the sides of the ridge) present a concavity outward is analogous to the inward curvature of the tip end of the shaft of the rib in the severe rachitic malformations of the costochondral junction when yielding inward is taking place.

It is, of course, dangerous to draw inferences from experiments on inanimate objects about phenomena which occur in living tissues. If, however, a patch of some not very bendable material, weakened in the middle by being partially split, is glued to the surface of a moderately distended rubber bag and the bag is then further inflated, the patch yields at the points of the split and along the line of the split is thrown into a ridge.

Though we are by no means certain that the explanation offered for the ridge formation and associated pathological conditions is the correct one, we believe it to be the most probable explanation. We think it must be assumed that the phonomena in question are the the result of forces acting from *within* a cranium in the process of growth, not of extraneous forces operating from *without* according to the explanation of Thoma.

ARE THE MALFORMATIONS GERMINAL IN ORIGIN OR ACQUIRED?

We are now in a position to consider the question: Are the deformities to be regarded as the results of defects inherent in the germ plasm, or as acquired during intra-uterine life through the operation of influences injurious to the embryo?

Are the Malformations Germinal?—At first thought it might appear that the occurrence in combination of malformations situated at widely separated and developmentally independent parts of the body was against an inherited and in favor of an acquired origin. It is evident, however, that combinations of defects may be transmitted in the germ plasm as readily as single defects, or different groups of characteristics, apparently unrelated to each other. There is an exceedingly well known congenital malformation transmitted from one generation to the other, which regularly involves two developmentally independent parts of the body. We refer to dysostosis cleidocranialis,[88] first described by Marie and Sainton.[89] In this combination of malformations the skull and clavicle are affected. The clavicle either appears to be absent on both sides (more rarely on one side only) or is represented by rudiments. The skull presents a variety of defects—persistence of certain parts in a membranous state, wormian bones, absence or aplasia of the nasal and lacrymal bones, underdevelopment of the skeleton of the face, a narrow and high palate, anomalies in implantation of the teeth, prognathism of the lower jaw, incomplete ossification of the base of the skull, etc. The brachycephaly and the platycephaly are characteristic. Associated defects in other parts of the body have been reported. Thus, it is seen that an inherited condition, dysostosis cleidocranialis, furnishes more than one analogy to the combination of defects under consideration.[90]

When, however, the histories of our cases are searched with the special object of determining an inherited origin, little evidence is forthcoming. There is no record of the existence of acrocephaly alone or with defective development of the extremities in other members of the immediate families, among forbears or collateral branches. Furthermore, with the exception of Dubrisay's patient who had imperforate anus, there is no record of any congenital malformation additional to those of the head and extremities. Moreover, with the exception of the case of Hutchinson[92] (Case 23) (the mother had given birth to a monster said to have had "a head like a cow"), there was no record of congenital malformation in the patient's immediate family, and with the exception of the case of Camus (one distant cousin had ankylosis of the elbows, and a sister of the cousin was an idiot) none in previous generations or in collateral branches. The case histories, therefore, afford almost no evidence in favor of the view that the malformations were inherited according to the mendelian law, and little evidence that they were the product of defective germ plasm.

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88. Hultkrantz, J. W.: (a) Ueber congenitalen Schlüsselbeindefect und damit verbundene Schädelanomalien, Anat. Anz., Jena **15**: 237, 1899. (b) Les altérations du crâne dans la dysostose cléidocranienne, N. iconog. de la Salpêtrière, Par. **21**: 93, 1908.

Sterling, W.: Die tropischen, vegetativen Erkrankungen, Missbildungen und Entwicklungshemmungen des Knochensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **9**: 1, 1914.

89. Marie, P., et Sainton, P.: Observation d'hydrocéphalie héréditaire (père et fils), par vice de développement du crâne et du cerveau, Bull. et mém. Soc. méd. hôp. de Par. **14**: 706, 1897; also: J. de clin. et de thérap. inf., Par. **5**: 405, 1897.

90. Another combination of congenital defects also involving the skeleton and occurring in members of the same family (two families were studied in two generations) has been described as a clinical entity by Dzierzynsky[91] under the title dystrophia periostalis hyperplastica familiaris. It is said to be characterized by an oxycephalic skull and shortening and thickening of the fingers, accompanied by deformities in the joints resulting in limitation of motion. From Dzierzynsky's description and illustrative photographs it is not clear to us that the conditions were well defined or even existed in all the instances in which Dzierzynsky thought they existed. The combination of defects described by Dzierzynsky ought not to be regarded as a clinical entity in the present state of knowledge concerning it. There is the possibility that some of his cases belonged to the group of cases which we are describing.

91. Dzierzynsky, W.: Dystrophia periostalis hyperplastica familiaris, Ztschr. f. d. ges. Neurol. u. Psychiat. **20**: 547, 1913.

92. Hutchinson, R.: Three Cases of Oxycephaly, Proc. Roy. Soc. Med., Lond., Sect. Dis. Child. **3**: 125, 1910. See also Fletcher [Discussion], p. 127.

In putting a valuation, however, on the absence of evidence pointing to an inherited origin it is necessary to remember that in a number of instances the family histories were incomplete and that in no single case had the subject of the malformation had children. Moreover, it must be considered that in an increasing number of instances oxycephaly and scaphocephaly have been reported in more than one child of a family or in two succeeding generations. Symmetrical syndactylism is one of the commonest inherited defects. So far as we are aware, familial syndactylism has never been accompanied by acrocephaly.

The evidences of polydactylism supplied by roentgenograms of the feet in the cases of Davis and Bertolotti and Boidi Trotti cannot be thought to indicate an origin in the germ plasm. Harrison,[45c] for instance, has found that removal of one-half of the fore limb bud in the amblystoma was sometimes followed by syndactylism, incomplete development or absence of a digit, of a hand or forearm but also by reduplication of a digit, of a hand (mirror image reduplication!) or of the entire limb. Also the almost complete reduplication of the deformities of the extremities on the two sides of the body in some of the cases (for example, the deformities of the bones of the feet in the patients of Bertolotti and Boidi Trotti (Case 12), Régis (Case 11) and our own cannot be taken to indicate a defect preexistent in the germ plasm. The injury may have taken place soon after fertilization has been accomplished or at a later period when the embryo was still composed, relatively speaking, of few cells and the cellular precursors of the future limb buds were still aggregated. It is impossible to imagine the production of identical deformities of the hands and feet, after the development of the limb buds had begun, if there is conceived to be on the two sides of the body a perfect correspondence of cell to cell in situation, metabolic state and formative impulse and an application of the injurious influence with a perfect impartiality. The almost complete correspondence of the complicated deformities indicates merely that the injury to the growing embryo must have been done at an early period in its development, if ever done at all.

Are the Malformations Acquired?—Davis saw in the malformations of the joints of the hands and feet in his case, as depicted in roentgenograms, the marks of an inflammatory process. Of course, if traces of inflammation can be identified in the hands and feet, it becomes probable that the malformations of the head as well as those of the extremities had an acquired origin. We are certain, however, that the deformities of the extremities, as revealed through the roentgen ray, do not show the marks of an inflammation and are confident that they exhibit no peculiarities that preclude an origin in defects or eccentricities of the germ plasm.

If the deformities of the skull and extremities themselves fail to give the clue to an acquired origin, the only hope of finding it would seem to lie in reading the riddle of their relationship to each other: Why should the skull and extremities be selected to be affected together? Is it possible to explain their selection on the basis of a common vulnerability?

There is some reason to suppose that the extremities of the fetus, in particular the ends of the extremities, are especially vulnerable. At least in young fetuses aborted in all probability as the result of injurious environmental influences (the abortion is usually ascribed to faulty implantation of the ovum), the extremities are often found to be undersized and the hands and feet retarded in development.[93] The heads of such fetuses also appear abnormal; they are undersized and, relatively speaking, flat. The limbs fail to show, however, on gross inspection, the syndactylous malformation which characterizes the cases of our series. Moreover, the stunting of the head was probably not due to a maldevelopment of the cranium, inasmuch as the latter at the time was composed chiefly of membrane. The brain is known to be a tissue of extreme vulnerability in fetal as well as postfetal life.

Of course, the base of the skull and the extremities are apparently in approximately the same stage of development at a period when the injury to the upper extremity conceivably may have taken place. The base of the skull begins to become differentiated in condensed mesenchyme at about the latter part of the fourth week and the hands and feet [94] at about the fifth and sixth weeks. It is probable that the primordial cranium vault is undergoing analogous changes simultaneously. Accurate information, however, concerning the very early development of the vault of the skull is lacking. We know merely that the membranous layer which forms the roof of the cranial cavity first becomes recognizable at the side of the head in embryos from 9 to 11 mm. long, and gradually extends until it covers the entire vault (Keibel and Mall [95]). If, now, the mesenchymal substance were especially vulnerable at the period when condensation was about to take place, some unfavorable environmental influence acting at the proper moment might injure both skull and extremities. The time relationships in the development of the skull and hands and feet, however, so far as we know them, are not exactly the same. Other parts of the skeleton in approximately the same stage of development at this period apparently are spared. That the mesenchymal substance is especially vulnerable at the time of its condensation or at any period is not proved. In general, mesenchyme and its derivatives, certainly the mesenchymal forerunners of the cartilage, and the cartilage itself, appear to be especially resistant. Finally, it is difficult to imagine what kind of an injurious influence could be operative at the same time on the primordia of skull and extremities. That the ends of the limb buds, composed of tissue destined to undergo more complicated development than the rest and farthest removed from the main body mass, might be especially apt to suffer is easy to understand, but not so easy why the cranium should be affected.

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[93] Dr. George L. Streeter, personal communication.

[94] The development of the lower extremity lags behind that of the upper.

[95] Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia and London, J. B. Lippincott Co. **1**: 548, 1909.

It is obviously impossible for us to reach a positive conclusion in regard to the source of origin of the combined malformations. We incline to the view, however, that they originated in defects in the germ plasm itself. The chief reason that we lean toward that hypothesis is because of the cases of oxycephaly and scaphocephaly in which there is the history of a familial incidence.[49, 65a, 92, 96] In a recent case report by Bedell,[96] all three children in one family were scaphocephalic. One of the three children had an abnormal condition of the left elbow[97] suggestive of a unilateral congenital malformation of the bones forming the joint, such as was present on both sides in a number of the cases of our series. If the fetal malformations of the skull characterized by a synostosis of the sutures are germinal in origin, we believe them germinal in origin when accompanied by defective development of the extremities.

SCAPHOCEPHALIC MALFORMATIONS OF THE SKULL ALSO MAY BE ACCOMPANIED BY SYMMETRICALLY DISTRIBUTED MALFORMATIONS OF THE EXTREMITIES

To the present point we have considered only acrocephalic malformations of the skull in relation to defective development of the extremities. Defective development of the extremities, however, also accompanies scaphocephalic malformations. We have found one such case in the literature and have ourselves seen one such patient. In the two subjects the scaphocephalic deformity of the cranium was well marked but the malformations of the extremities were extremely slight. In the case reported by Küttner[98] (Case 29) the statement is made that "with the exception of insignificant malformations of the thumbs and great toes the body is essentially normal."[99] In the child seen by us (Case 30, Fig. 25) there was some congenital malformation at the elbow joints which rendered complete extension impossible (Fig. 26). In both cases there was an internal hydrocephalus.

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[96] Bedell, A. J.: Oxycephalus: Report of Three Cases with Operation in One, J. A. M. A. **68**: 1979 (June 30) 1917. Weiss, L., and Brugger, O.: Oxycephaly and Disease of the Optic Nerve, Arch. Ophth. **24**: 55, 1895. Hanotte, M.: Anatomie pathologique de l'oxycéphalie, Paris, 1898, Masson & Cie., p. 85.

[97] "The left elbow joint resisted full extension, and when forcibly extended deflected outward with the inner condyle especially prominent," Bedell,[96] p. 1981.

[98] Küttner, H.: Der angeborene Turmschädel, München. med. Wchnschr. **60**: 2209, 1913.

[99] Page. 2208.

We are under the impression that severe malformations of the extremities occur less frequently with scaphocephaly than with acrocephaly, and we should judge from the relative numbers of reported cases in the literature, which have come to our notice, that the association with acrocephaly is more frequent than with scaphocephaly. Again, however, we are under the impression that the acrocephalic malformations of the cranium tend to be more extensive than the scaphocephalic malformations. If such be the case, it would be natural to expect more extensive malformations of the extremities in acrocephaly than in scaphocephaly, and that the association might be more common in case of the acrocephaly malformation of the cranium than in the case of the scaphocephalic malformation. We know of no instance of malformation of the extremities in association with trigonocephaly.

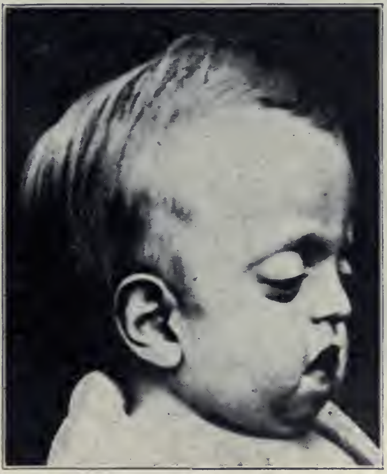

Fig. 25.—Photograph of head of W. F., authors' case of scaphocephaly and malformation of elbow joints (Case 30).

THE SIGNIFICANCE TO BE ATTACHED TO THE OCCURRENCE OF MALFORMATIONS IN COMBINATION

It now remains to point out the probable significance to be attached to the occurrence together of the malformations of head and extremities. Is the combination of malformations to be regarded as a clinical entity? Typical acrocephalic and scaphocephalic malformations without malformations of the extremities are frequent and malformations of the extremities similar to those in our series of cases exist apart from malformations of the skull. The association, therefore, is not constant. In spite of that fact, it might still be possible to regard the combination as a clinical entity, if, when the malformations occurred together, they always occurred in some definite form, intermediate between the malformations of the head with normal extremities on the one side and the malformations of the extremities without cranial defect on the other. The malformation of the extremities, however, shows the greatest variation. In some cases the hands and feet are the seat of most extensive maldevelopment and the bones entering into the formation of the elbow joints and apparently also the shoulder joints are involved. In other cases the malformation is limited to the bones forming the elbows or to most minor defects in the hands and feet. In other words, the malformation of the extremities occurs in a series of grades of severity from the most extensive deformities to the normal condition. There is some indication that the malformation of the head likewise occurs in all grades of severity from the most extensive to a condition differing but slightly from the normal. In the present state of knowledge, therefore, it seems unjustifiable to regard the combination of malformations of head and extremities as a clinical entity. The significance of their occurrence together appears to be merely an inconstant association. The malformation seems to have the special tendency, when appearing in the head, to appear also in the extremities. We believe, therefore, that it is necessary to think of acrocephalic and scaphocephalic malformations existing alone and acrocephalic and scaphocephalic malformations existing in combination with symmetrically distributed malformations of the extremities, not as distinct things, but as different expressions of one and the same thing. Accordingly we have felt obliged to discard the title, "acrocephalosyndactylism." [100]

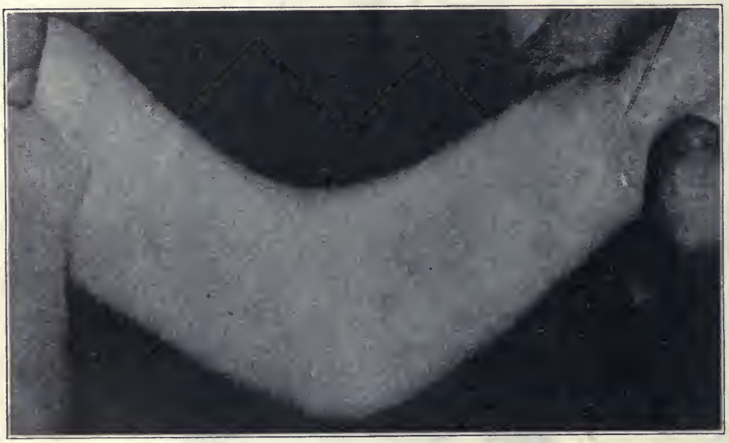

Fig. 26.—Photograph of elbow of W. F., illustrating maximum degree of extension obtainable (Case 30).

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[100] The title, "acrocephalosyndactylism," does not include those cases in which the malformation of the extremities was limited to parts other than the hands and feet.

We believe that the association of deformities of the extremities with deformities of the skull of the kind under consideration is more frequent than hitherto has been thought or than statistics indicate, and that in some subjects of oxy- and scaphocephaly unsuspected maldevelopments of the extremities will be brought to light if the possibility of their occurrence is kept in mind. We are not certain that more careful studies may not reveal in association with the maldevelopments of the skull maldevelopments in yet other parts of the skeleton than the extremities.

In conclusion, we wish to express our indebtedness to Dr. Warren Lewis and Dr. George L. Streeter of the Department of Embryology, Carnegie Institute of Washington, for their suggestion of ideas, their constant interest, and their many acts of courtesy. Without their cooperation the study in its present form would have been impossible. We wish to express our thanks to Dr. A. H. Schultz of the same department, for his great kindness in taking the measurements and for his advice on a number of occasions. We wish also to express our thanks to Dr. J. W. Pierson of the Department of Roentgenology for assistance in the interpretation of the roentgenograms.

ABSTRACTS OF CASES

I. CASES OF ACROBRACHYCEPHALY WITH COMPLETE OR ALMOST COMPLETE SYNDACTYLISM

(Cases 1 to 20, inclusive)

Case 1.—Troquart,[23] 1886. New-born child, delivered at term after normal labor. Mother 33, father 31 years old. Both parents always well; neither they nor grandparents deformed. Hands of baby in condition of almost complete syndactylism apparently with some osseous union. Thumbs separate. Feet showed same condition. Head voluminous; frontal bosses prominent; anterior fontanel extended almost to bridge of nose. Partial separation of soft palate. Dudon, in discussion of Troquart's case, referred to sutures as open, and stated that aspect of child was that of hydrocephalic. (Description meager; no photographs; no roentgenograms.)

Case 2.—Beno,[101] 1886. Healthy, well nourished girl, 18 months old. No history of malformation in antecedents. Head greatly flattened from before backward. Sutures closed. Forehead prominent in upper part. Eyes protruded slightly. Dentition normal. Feet in condition of complete syndactylism without bony union, not interfering with walking. Fngers and thumbs of both hands fused into single mass. On palmar surface of hands tips of three fingers marked out by shallow grooves; on dorsal surface all fingers delineated by longitudinal grooves. One nail served for second, third and fourth fingers, and rudimentary nail for fifth. All metacarpal bones and phalanges seemed to occupy normal positions and to be unattached to each other except terminal phalanges, which appeared joined into single mass, and except metacarpal bones of thumbs which were joined to corresponding index fingers by bony and fibrous union. (Description brief; no photographs; no roentgenograms.)

Case 3.—Magnan and Galippe,[11] 1892. Man, 35 years old. Only statement made in regard to family history is that on maternal side there was history of alcoholism and nervous disorders. Head flattened in front and behind and asymmetrical. Right frontal eminence exceedingly prominent, left flattened; left mastoid region prominent, right poorly developed. Forehead broad; much higher on right side than on left; traversed in middle portion by horizontal groove, above which in median line was well marked prominence. Occipital protuberance unusually large. Head particularly high about bregma so that "certain degree of acrocephaly" existed. Face appeared very flat, cheeks sunken. Nose large, thick, deviated to left. Nostrils small. Eyeballs so prominent they looked pedunculated, and protruded 1 cm. beyond plane of forehead. Sclera visible, especially inferiorly. Palpebral fissures directed downward and outward. Mouth distorted. Alveolar processes close together, converging anteriorly. Palate narrow, highly arched; soft palate exceedingly long, uvula bifid. Lower jaw narrow, as if compressed laterally. Teeth abnormally placed. Complete syndactylism of feet, and hands with exception of terminal phalanges of little fingers which were separate. Metacarpal bones of thumb, index and middle fingers could be distinguished and were not united, but those of third and fourth fingers were joined together behind. All phalanges seem to have been present, but last two phalanges of ring finger atrophic. Separate nails for thumb and little finger, but nails for index and middle fingers fused; rudimentary nail for ring finger. Deformity of left hand corresponded in general to that of right. Separate nail for great toe but nails of other toes united at edges. Arms not normal for complete extension, supination and certain other movements impossible. (Well described; photographs of whole body and of palate on page 19 of Gadelius' report; no roentgenograms.)

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[101] Beno, J.: Essai sur la syndactylie congénitale, Nancy, 1886, No. 238.

Cases 4 and 5. — Wheaton,[17] 1894. One case was illegitimate first child, aged 3 months at time of death; other, fourteenth child in healthy family dying when 2 months old. Deformities almost identical. We quote Wheaton's report:

> The deformity of the crania is characterized by arrest of development of the base of the skull in an anteroposterior direction, the fossae at the base of the skull being markedly contracted in an anteroposterior direction, but of about normal width from side to side. The posterior fossa of the skull is especially narrow from before backwards, and the occipital bones are extremely small. The basi-occipital bone in one case is only one eighth of an inch in diameter and in the other case this portion of the occipital bone is united to the basisphenoid by firm bony union. The occipitofrontal diameter of the crania is only four inches in each case, whereas in the case of a new-born infant this diameter is four and a half inches. The biparietal diameter of the skull is also almost exactly four inches in each case, so that the cranial cavity is almost perfectly globular in shape. A continuous suture extends from the posterior fontanel to the root of the nose in both cases, and the frontal suture is especially wide, measuring an inch and a quarter in a transverse direction. There are wormian bones in the posterior fontanels in both specimens, and in the frontal suture in addition in one specimen. The margins of the bones bounding the sutures and fontanels are irregular and have a crenated outline; the frontal and parietal bones in both specimens present numerous pits or elliptical depressions on their inner surfaces, where the bone is extemely thin, and in a few places bony deposit over these areas is absent entirely. These areas can be well seen when the bones are held in front of a light. During life the bones of the vault of the skull could be indented with the finger. With regard to the condition of the hands and feet, in both children the fingers of both hands were fused into one mass, but the thumbs were separated. The hands were not dissected, but in one child the metacarpal bones and phalanges of the two middle fingers appeared to be fused into one bone, and in the other case there were only four metacarpal bones and the second finger had no phalanges. The nails of the two middle fingers of both hands were fused into one in the case of one infant, and those of the three inner fingers were fused in the case of the other. All the toes were fused together in one child, but in the other the big toes were separate. The nails of the toes were separate in both cases. Talipes varus was present in both.
>
> During life the children presented the appearances of cases of hydrocephalus, except that there was no enlargement of the skull; but on postmortem examination no accumulation of fluid was found either on the surface of the brain or in the cerebral ventricles.
>
> Owing to the defective development of the occipital portion of the skull, the back of the head appeared to be nearly flush with the nape of the neck, the fontanels and sutures were tense, and the pulsation of the brain could be seen and felt through them. The bones of the face appeared to be normal, with the exception of those of the nose, which was very flat and depressed. The skin of the body, and especially that of the face, was very much wrinkled and of a yellowish color, and both children suffered from snuffles, the ears were wrinkled and small, and the tongue constantly protruded — so that the children had a very repulsive appearance. The children could not suck, and were fed by hand. Both children died from asthenia, without the development of any noteworthy symptoms.
>
> On postmortem examination the brain appeared to be compressed, and bulged considerably when the dura mater was incised; but, as before mentioned, there was no accumulation of fluid inside the skull. The convolutions were flattened as if from pressure, and the anteroposterior diameter of the brain remarkably shortened, in a manner corresponding with the shape of the cranial cavity. There was a marked want of development of the occipital lobes of the brain, which were so small that the cerebellum was almost entirely uncovered. The frontal lobes were also small and pointed. No important convolutions appeared to be absent, however. No other changes were found in the bodies except enlargment of the liver and spleen, in both instances the latter organ being tough and firm, evidently from excess of fibrous tissue. There were no signs of rickets.

(Necropsies; no photographs; no roentgenograms.)

Case 6.—Maygrier,[19] Fournier,[20] 1898. New-born girl. Mother had borne four healthy children to first husband. Second husband aged 35 years, had acquired syphilis at 19. Following marriage to second husband, two miscarriages in succession, next an apparently healthy child dying from intercurrent illness at 3½ years, finally patient. In second month of pregnancy with patient, abdomen noticed to be unduly large; by seventh it began to assume extremely large proportions. Labor occurred at term; unusually large quantity amniotic fluid. Birth instrumental. Forehead of child exceedingly prominent, protruding forward in middle part 2 cm. in form of very large tumor elongated from above downward, beginning at anterior fontanel and ending abruptly just above root of nose; at sides limited by inner borders frontal bones. Latter separated distance of 2 cm. and apparently displaced forward and outward by tumor. Head flattened in both temporal regions and behind to such extent that back of head appeared in same plane as neck. Sagittal suture narrow in anterior part but in middle broadened so as to form accessory lozenge-shaped fontanel between anterior and posterior fontanel. Anterior fontanel 4 cm. wide; posterior extremely wide. Eyes, unusually prominent, appeared more so than actually because of depression of superciliary arches. Palate formed high arch. All four extremities well formed with exception of hands and feet. Malformations hands limited to fingers. Thumbs flattened and shaped like spatulae, appeared dislocated internally and lay flexed across hollow of palm. Integrity movements thumbs preserved. Four fingers united in entire extent. Phalanges index, middle and ring fingers terminate in single mass of bone, surmounted by single nail; the proximal and middle phalanges separate. Phalanges of little finger, which has separate nail, not joined to others. Toes apparently united only by soft parts; each has nail. Child living one month after birth. (Magrier and Fournier each reported this case separately; photograph in Fournier's report; no roentgenograms.)

Case 7.—Ireland,[27] 1898. "Young man" (age not stated); fourth of eight children. Brothers and sisters healthy. No record nervous disorders or deformities in family. Slow in learning to walk and speak. At 14 sent to school for imbeciles where he learned joiners' work. Apparently under normal in intelligence. Head prolonged upward, narrow from before backward; circumference 55 cm. Eyes prominent, injected from imperfect closure of lids. Eyeballs have divergent axes. Skin thick, pustulated; deep furrows across forehead. Nose "shapeless." Lips broad. Mucous membrane of palate divided by longitudinal folds with apparently deficiency of palate bone behind. "The feet are short and broad, the first metatarsal bone is wanting on both feet and the first phalanx of the great toe is implanted in the angle between the second metatarsal and the internal cuneiform. The four outer toes have completely grown together with the soft parts. The feet are short and broad with high insteps." Hands, as shown in photographs, appear completely syndactylous. Arms are obviously abnormal for they reach only to level of pelvis. (Description fragmentary; no roentgenograms; photographs of front view of head and of hands in Ireland's book; these photographs and a lateral view of head and of whole figure in Gadelius' report, p. 18.)

Case 8.—Dubrisay,[24] 1898. New-born girl; weight, 3,150 gm.; length, 45 cm. Family history negative; no record of any malformation among antecedents or collaterals. Excess of amniotic fluid present at birth. Back of head normal. Anterior part projected forward; maximum deformity at summit frontal bone. Frontal bosses prominent; metopic suture 2 cm. wide, continuous with anterior fontanel. Root of nose depressed. Eyes prominent. Buccal cavity normal. Extremities well formed, with exception hands and feet. Metacarpal bones separated by well defined depressions; fingers fused into cone-shaped mass. No division between phalanges determined. At distal end of cone-shaped mass skin replaced by two nails unequal in size, one corresponding apparently to nail of thumb, other to nails of fingers. Both hands affected in same way. Toes formed single mass but nails formed uninterrupted band extending from one side to other. Roentgenograms of feet and hands showed metacarpals normal but phalanges replaced by two masses of bone, separate, apparently representing fused phalanges; metatarsal bones united in certain places. In addition to deformities enumerated imperforate anus. Died six days after birth. (Necropsy, but skull and extremities not examined. Description very poor. Photographs; roentgenograms of extremities but not of head.)

Case 9.—Camus,[21] 1903. Boy 10½ years old, oldest of three children; other two normal. Family history negative except one distant cousin had congenital ankylosis of elbows and sister of cousin idiot. Head much prolonged in vertical direction but short, flattened at sides. Forehead, exceptionally high, presented in median line keel-shaped enlargement especially prominent in lower part; in contrast frontal eminences depressed. Supra-orbital arches prominent. Parietal bones extended abnormally far upward; not convex as usual; separated from squamous portions temporal bones which seemed very prominent by depression. Bones of vault of skull thick and resonant. Face had flattened appearance through atrophy of malar and superior maxillary bones. Nose short, not very prominent, deviated to left. Eyes protruded; palpebral axes oblique from within outward and downward. Examination buccal cavity disclosed atresia superior maxilla which, maximal anteriorly, was cause of well developed acrognathia. Alveolar processes and mucous membranes covering them hypertrophic in region of incisor teeth and joined in such way as to produce recess in anterior portion of roof of mouth. Soft palate cleft. Hands showed syndactylism of all four fingers but with thumbs free. Latter had own nails but phalanges fused into single place. Fingers united in such way as to form spoon-shaped mass. Ring, middle and index fingers had single nail, and distal two phalanges of all three appeared fused. Fifth finger having nail joined to others only through union of soft parts. Feet showed complete syndactylism consisting in fusion of soft parts alone. Each toe had own nail. Ankylosis of elbow joint in semiflexion and pronation ascribed to "synarthrosis" of humerus and radius, with hypertrophy of head of latter. (Fair description; no photographs; no roentgenograms.)

Case 10.—Apert,[1] 1906. Girl, aged 5 months. No information regarding child's antecedents or mother's pregnancy. Head very high; forehead ascends vertically but rounded and bulging forward beyond vertical in upper half; across middle portion horizontal groove. Superciliary ridges prominent. Eyeballs protruded. Anterior fontanel occupied summit of head. Immediately behind anterior fontanel head fell off abruptly to neck, so that occiput perfectly flat. Palate cleft in posterior part; uvula bifid. Thumb of left hand almost normal but spatula-shaped, lay transversely across hand. Three other fingers besides thumb; outer two firmly united, apparently by bony union; nails fused. Inner one joined to other two only by soft parts; moveable independently of latter. Three fingers of this hand almost immobile on metacarpals, and ankylosed at phalangeal joints. Deformity of left hand almost exactly like that of right, except little finger entirely free. Right foot had four toes, of which great toe short, flat, mobile, two middle toes fused, immobile, little toe flat, mobile, provided with large Hippocratic type of nail; left foot had five toes joined together, big toe loosely, other four firmly. Four nails fused at points of contact. (Incompletely described; no photographs; no roentgenograms.)

Case 11.—Régis,[31] 1914. Under legend "Dégénérée avec stigmates physique multiples de dégénérescence" author publishes photograph of girl, certainly 16 years old, showing characteristic deformity of head and extremities. Top of head hidden by cap, but forehead high, face broad, eyes far apart and protruding, especially left, and having divergent axes. General contour of face typical. Hands and feet syndactylous. Thumbs free, but fingers united. Great toes free, but others joined together. Roentgenograms indicate malformation more extensive in hands than feet. Metacarpal bones of little and ring fingers represented by thick, irregularly shaped, single bone. Phalanges consist of single bones about two-thirds length of metacarpal bones which incline toward each other and are fused at distal extremities. Phalanges of thumb represented by single nodular mass which joins metacarpal bones on inner side of distal extremity. Bones of carpus and wrist cannot well be seen. Phalanges and metatarsals of feet not united laterally. Metatarsal bones abnormally formed, that of great toe being huge. Feet broad. Metatarsal of great toe directed forward and inward, metatarsal of little toe forward and outward, so giving to foot fan shaped appearance. Little toe has long proximal and short distal phalanx, others have single phalanges.

Evidences of degeneration cited are: Obesity, thickness of hair, macrocephaly, asymmetry of face, exophthalmus, flattening of root of nose, narrow and highly arched palate, absence of soft palate, anomalies of implantation and form of teeth, prognathism, syndactyly, enlargements of breasts. (Photograph of whole body; roentgenograms of hands and feet.)

Case 12.—Bertolotti and Boidi Trotti,[12b, c] 1915. Girl 5 years old. Father, mother, two sisters, one brother well. One sister dead of "meningitis." No history syphilis. No deformities similar to those of patient known in family. "Abundant" amniotic fluid present at birth. Head oxycephalic; vertical diameter greatly increased; sagittal diameter comparatively diminished. Frontal bone very high with deep transverse groove in middle portion above protruding superciliary arches. Forehead bulges markedly above transverse groove. Bregma at apex of skull in same vertical plane with face. Skull slopes downward from bregma to occiput. Skull protuberant in temporal and constricted in mastoid regions. No occipital prominence. Occiput neck in same vertical plane. Metopic suture closed; synostosis marked by prominent ridge. Face broad and full in upper and zygomatic portions, decidedly pinched inferiorly. Eyes obliquely placed, palpebral fissures directed downwardly and outwardly from nose at angle of 120 degrees. Exophthalmus. Optic neuritis; margins disks blurred; veins large and tortuous. Acuity vision diminished. Ears large, regular in form. Otoscopic examination reveals no abnormality. Acuity hearing diminished, due, it is stated, to some defect in central nervous connections. Middle portion upper lip prominent; angles mouth depressed. Lower lip retracted; chin recessive. Marked atresia of maxilla. Palatine vault high and angular. Uvula and soft palate divided but palatine eminences seem united. Dentition very irregular; some incisors directly back of others. Palatine tonsils large. Adenoids present. Nasal fossae narrow, deviation to left. Nasal obstruction. Circumference head at level superciliary arches, 49 cm., at transverse frontal groove, 47 cm. Maximal sagittal, 13 cm., maximal transverse, 15 cm. Cephalic index, 115. Roentgenographic studies of cranium show vault considerably thinned; digitations marked especially in frontal region. Cranial vault very high, relatively short in sagittal diameter. Base "scooped out" with wings of sphenoid more nearly vertical than usual and median cerebral fossae very deep. Orbital fossae shallow; vertical diameters greater than horizontal. Sphenoidal angle, 168 degrees instead of normal—132 degrees. Diastasis of suture between body of sphenoid and basi-occipital bone.

Hands show five digits formed from single spoon-shaped mass as result of operation. Digits separate for only short distance distally; simply grooved off from each other proximally. Body of hand narrow; digits irregular and bulbous, especially at ends. Fingers flare in fan-like manner. Each digit has own nail; nails large, hypertrophic. Before operation nails, except nail of thumb, completely fused. Roentgenographic study shows partial ossification of carpal bones (six nuclei on right, five on left), partial fusion of fourth and fifth metacarpals and normal metacarpal epiphyses. Thumb has but one phalanx; three phalanges for each finger, although phalanges are fused in several digits. Two distal phalanges very large and bizarre in shape; epiphyses also very large. Limitation of movement at scapulo-humeral articulations and elbows; synostosis between radius and ulna at elbow.

Feet show complete syndactylism (no surgical interference). Slight grooves between first, second, fourth and fifth toes. Nail for great toe divided; four other nails on each foot. Ossification of tarsus normal but some of the bones abnormal in shape, size and relations. Some metatarsals bifurcated and fused with neighboring bones. Phalanges grossly misshapen; apparently only two for each digit. Large epiphyses.

Intelligence average or even above. Evidences of rachitis. (Well described; photographs and roentgenograms of head, hands and feet.)

Case 13.—Davis,[14] 1915. Father and mother living, well; three other children, all healthy; two miscarriages. No mention made of malformations in family. Patient, girl, 3½ years of age; born at term without instruments, "puny" until 1½ years old; probably mentally retarded. Head shortened in sagittal diameter; frontomental, bitemporal and bizygomatic diameters increased; shape of head that of foursided pyramid with apex in region of lambda and base formed by diamond-shaped face; face broad, flat; forehead high, precipitous; superciliary ridges highly arched and flattened. Bridge of nose "low," and bulging. Ten teeth, well formed but irregularly placed. Hard palate highly and sharply arched; apex of inverted "V" near soft palate; shelf-like projection along alveolar margins of maxilla. Proptosis. Ophthalmoscopic examination shows media clear, nerve head gray, margins of disks blurred; apparently some swelling of disks but could not be measured; retinal vessels slightly tortuous. Measurements: circumference (fronto-occipital), 48 cm.; fronto-occipital diameter, 15 cm.; bitemporal, 12 cm.; biparietal, 14.5 cm.; length of frontal suture, 9 cm.; width of frontal suture, 4 cm.; cephalic index, 96.6. Photographs after plastic operations show three digits on left hand, three on right with shadows suggestive of fourth; medial digit in line with axis of arm; lateral digits flare out from this axis; digits fused at base and only free for short distance distally; they have constricted, pinched off appearance at metacarpal phalangeal junction in comparison with broader body of hand; hands operated on during first year; all digits of each hand were so completely fused that no line of cleavage could be made out. Feet show no abnormality above metatarsophalangeal articulations; no digits; nails continuous with each other: five on left foot, four on right: great toe portion stands out prominently and is turned up dorsally as is whole phalangeal region of foot. Roentgenograms. Head: sagittal, lambdoid and coronal sutures closed; metopic suture enormously dilated: sella turcica deepened and broadened: orbits fore-shortened: digital impressions marked in occipital and posterior positions of parietal bones. Right hand. Five metacarpals, fourth and fifth partially fused: five digits: for thumb one bone; for second digit three bones, terminal one being curved back and possibly belonging to thumb: bones of third and fourth digits closely opposed and joints replaced by bone: three phalanges for fifth finger, second and third falling laterally. Left hand. Five metacarpals, fourth and fifth partially fused. No bone shadows for thumb, second, third and fourth fingers "present bone shadows suggestive of a phalangeal complement for four fingers. This fact probably accounts for the bones missing from the thumb. These bones irregularly fused into bony plate with apparently obliteration of proximal interphalangeal joints. In little finger shadows of but two bones. There is gap at position which the middle phalanx should occupy." Right foot. Tarsal bones normal: six metatarsals; first and second partially fused. "The first is incomplete proximally, while distally it appears to extend without division or other trace of phalanges into the great toe." Fourth and fifth metatarsals partially fused. Phalangeal rudiments for six toes. Left foot. Similar to right; union between first and second metatarsals more "intimate"; no other union between metatarsals. First and second phalangeal rudiments closely united. (Good description: photographs and roentgenograms of head, hands and feet.)

Case 14.—Gadelius,[10] 1915. Man, 24 years old; illegitimate. Parents not deformed. Subsequent to birth of patient mother married another man and bore normal child. Deformities fully developed at birth. Head "cylindrical," flattened from before backward and prolonged upward. Circumference at root of nose, 54.3 cm. Fronto-occipital diameter, 16.5 cm.; biparietal, 15.5 cm. Cranial index, 94. Eyeballs protruding in downward outward direction; divergent; right eye does not coordinate with left. Nose short, broad. Prognathism lower jaw. Hard palate cleft; soft palate intact. Teeth regularly placed. Hands and feet syndactylous. Middle three fingers form single mass; thumbs free, little fingers partially free. Roentgenograms of hands show metacarpal bones separate from each other, approximating normal in contour. Little fingers have three bones, proximal abnormally long, middle abnormally short and thick; ring fingers two bones, proximal almost as long as metacarpal, obviously representing proximal and middle phalanges fused; middle finger of right hand single irregularly shaped bone, obviously representing all three phalanges; middle finger of left hand to be described presently; index fingers have two bones, distal representing two distal phalanges fused. Single nodular mass of bone represents phalanges of thumb, it joins metacarpal bone at inner side of its distal extremity. Bones of index, middle and ring fingers, right hand, fused together distally from point corresponding to junction of middle and proximal phalanges. Index finger of right hand connected with ring finger by horizontal bridge of bone of about same thickness as phalanx. Bone representing proximal and middle phalanges of middle finger directed downward and inward overlies long bone representing proximal and middle phalanges of ring finger; bone representing distal phalanx of middle finger, not connected with bone representing proximal and middle phalanges, projects downward from bridge of bone just mentioned. Toes partially syndactylous. Roentgenograms show syndactylism of toes limited to soft parts. Metatarsal bones approximately normal with exception that of great toe, which is much thickened and irregularly shaped. Little and fourth toes have two bones each, proximal probably representing first two phalanges; third and second toes single bones, obviously representing all three phalanges; great toe one large irregular mass of bone, in excavation in side of which lies loose fragment. Foot extremely broad. Metacarpal and phalanx of great toe directed forward and inward. Mental development lower limits of normal. (Photographs of whole body and of hands: roentgenograms of hands and of one foot.)

Case 15.—Gadelius, 1915. A girl, age not given, apparently about 6 years old when examination was made. Parents healthy; not deformed. Patient eleventh child. Brothers and sisters normally formed. Development somewhat retarded. Walked at 2 years. At 6 years sent to home for defective and crippled children. On examination, striking features head and extremities. Head high. Circumference, 47 cm. Fronto-occipital diameter, 16 cm.; biparietal, 14.5 cm., cranial index, 90. Eyes far apart. Marked proptosis. Horizontal axes of eyes directed downward and outward. Palate cleft. Syndactylism of hands and feet but thumbs and great toes free. Roentgenograms of hands indicate that phalanges are represented by single bones fused together distally. Metacarpal bones apparently separate. Died at age of 12 years. (Photograph of whole body: roentgenograms of hands.)

Case 16.—Gadelius, 1915. A boy, age not given, apparently about 8 years old when examination was made. Four brothers and sisters. All members of family, including parents, healthy, normally formed. Head shows marked brachy and acrocephaly. Marked exophthalmos with characteristic rotation eyeballs; axes in downward and outward direction; external strabismus. Palate cleft. Breathes with mouth open. Eyes inflamed; cornial ulcers. Feebleminded. Syndactylism of hands and feet but with thumbs free and great toes partially free. Roentgenograms indicate that metacarpal bones, though not normally formed, are separate from each other. Phalanges, including those of thumb represented by single bones. Those of fingers fused together distally into single mass. Roentgenograms of foot indicates less marked degree of malformation. Phalanges represented by two bones each with exception of great toe which is represented by large mass of bone shaped like horse shoe. Phalanges of toes not united laterally. Patient died at 8 years. (Necropsy, but no report of findings in skull or extremities; hypophysis studied microscopically and found to be normal: photographs of head and hands: roentgenograms of one hand and one foot.)

Case 17.—Gadelius, 1915. Woman, 25 years old, eldest of three children. All members of family, including parents, normally formed. Marked acrocephaly and brachycephaly. Exophthalmos with peculiar rotation of eyes in downward and outward direction. Cleft palate. Prognathism of lower jaw. Abnormalities in implantation of teeth. Syndactylism of all four extremities. Intelligence subnormal. (Meager description; photographs of head, palate, hands and feet; no roentgenograms.)

Case 18.—DeSalterain,[29] 1917. Negress, 8 years old. Parents healthy. Eight children previous to birth of patient, of which four had died, one at birth, one during first year (unknown cause), other two in adult life. No member of family with exception of patient deformed. Born at term in mother's forty-sixth year. Deformities head and extremities present at birth. Except for convulsions at 6 years and again at 7 years always well. Striking feature shape of head. Latter "prolonged upward," markedly shortened from before backward. Length and breadth, each 16 cm.; cranial index, 100, circumference, 51 cm. Glabella depressed. External occipital protuberance not felt. Exophthalmus especially marked on right side. Left fundus shows pallor disk and enlargement in transverse direction: right not visible on account staphyloma. Hard palate highly arched, marked by central longitudinal ridge. Adenoids hypertrophied, tonsils present. Syndactylism both hands. No statement made to indicate if feet similarly affected. Height normal. Mental development backward. Roentgenogram of skull said to have shown prematurely ossified sutures, deepening of fossae in addition to brachycephaly. Wassermann negative. (Photograph of head: roentgenogram of head referred to but not shown: roentgenograms of extremities.)

Case 19.—Ruh,[16] 1916. Father and mother living; two other children, living and well; no miscarriages, no history of syphilis; no malformation in "any member of the family" (report not specific); deformity in patient attributed to "maternal impression." Patient a boy, 6 months of age; admitted to hospital for "cold in the head"; born at term; weight, 8 pounds; delivery normal but child resuscitated with difficulty; weaned at 2 weeks because difficulty in breathing prevented nursing. Well nourished child with normal mentality. Head shows increase in measurement from nasion to inion: biparietal and anteroposterior diameters decreased, whereas bitemporal and bizygomatic diameters increased. Circumference (fronto-occipital), 38 cm.; fronto-occipital diameter, 11 cm.; bitemporal, 11.5 cm.; biparietal, 10.5 cm.; cephalic index, 95.6. Pronounced bulging of forehead in superior portion and flattening of superciliary arches above which is transverse groove. Occipital region much flattened; no external occipital protuberance. Anterior and posterior fontanels, coronal, sagittal and lambdoid sutures open: metopic suture replaced by ridge-like bony prominence. Veins of scalp, especially temporal much distended. Ears large; external auditory canal compressed anteroposteriorly so that examination of ear drums is impossible; sense of hearing acute. Eyes obliquely placed so that external canthi lower than inner: proptosis. Base of nose depressed. Palate narrow, highly and acutely arched; mouth kept open; tongue larger than normal, protrudes because of shortening of pharynx; uvula normal. Roentgenogram is said to show digital impressions in frontal and parietal regions. Hands: complete syndactylism, excepting thumbs, partially flexed at the metacarpophalangeal joints: palms spoon-shaped: nails fused. Roentgenogram of right hand shows absence terminal phalanges: metacarpals not fused: considerable ossification of unciform and os magnum.

In left hand fusion of fourth and fifth metacarpals. Feet show complete syndactylism including great toes. Nails not completely fused as in hands. Roentgenogram right foot shows no terminal phalanges: first digit larger than normal and on inner side notch—at base of second metatarsal large tuberosity. Roentgenogram left foot shows absence terminal phalanges: first digit much larger than normal. Near base second digit large sesamoid bone: first and second metatarsal bones united near bases. (Photographs of head and extremities: roentgenograms of feet and hands: roentgenogram of head referred to but not shown.)

TABLE 4.—MEASUREMENTS OF SKULL AS COMPARED WITH MEASUREMENTS OF SKULL OF NORMAL NEW-BORN CHILD

	Skull of Rieping's Case	Skull of Normal New-Born Child*
Suboccipital bregmatic diameter	90 mm.	90 mm.
Fronto-occipital diameter	80 mm.	110 mm.
Mento-occipital diameter	110 mm.	130 mm.
Vertical diameter (vertex to base)	105 mm.	95 mm.
Biparietal diameter	60 mm.	90 mm.
Bitemporal diameter	95 mm.	80 mm.
Projective ear height (tragus-vertex)	95 mm.	80 mm.
Intermalar breadth	50 mm.	65 mm.
Maximum horizontal circumference	31 cm.	34 cm.
Maximum vertical circumference	34 cm.	35 cm.
Length-breadth index	87.5	72.72
Depth of orbital fossae	18 mm.	28 mm.†
Depth of cerebral fossae (measured from highest point of cranium)		
Anterior cerebral fossa	19 cm.	19 cm.
Middle cerebral fossa	23 cm.	22 cm.
Posterior cerebral fossa	28.5 cm.	26.5 cm.
Anterior border of crista galli to posterior border of posterior fontanel	16 cm.	21 cm.

* Apparently these measurements are quoted from Schauta.

† Apparently these measurements were made by Rieping on a normal skull. [Necropsy: photographs of head, front and lateral views. No roentgenograms].

CASE 20.—Rieping,[15] 1919. Family history not known. Child seen only after death. Body normal everywhere with exception of head and extremities. Head oxycephalic. As seen from in front after removal of scalp (photograph), face appears as if surmounted by casque helmet. Highest point of head forms a peak situated about midway between fontanels and immediately above external auditory meatus. Occipital portion of head less prominent than normal but not flat as in majority of cases. Anterior fontanel is 10 mm. long and 20 mm. wide. Posterior fontanel much larger than anterior; shaped like equilateral triangle, measuring 40 mm. across base, and 50 c.c. in length (the perpendicular). Metopic suture "wide open" from level of superciliary ridges to anterior fontanel, from which it is separated by small bony bridge. It contains wormian bone 40 mm. long and 6 mm. wide. Sagittal suture divided into limbs by oxycephalic peak. Anterior limb exhibits interserration of opposed edges of parietal bones, which are overlapped and raised into keel-shaped ridge (crista sagittalis). Posterior limb shows interlocking in upper part but in lower part spreads open as it passes into posterior fontanel. (For continuation of description of skull, see pages 259 and 260.) Eyes not described. Lidslits, however, slant in characteristic manner from within outward and downward (photograph) and prominence of lids makes it almost certain that eyeballs beneath protruded. Hard palate highly arched but not cleft. Uvula and soft palate normal. Fingers and toes completely united. Nail formation irregular. No roentgenographic studies or dissections of hands or feet.

II. CASES OF ACROBRACHYCEPHALY WITH RELATIVELY SLIGHT DEFORMITIES OF THE EXTREMITIES

(Cases 21 to 24, inclusive.)

CASE 21.—Dodd and McMullen,[18] 1903. Boy, 7 years old. Deformities present at birth. Third child in family of four; others healthy, normally developed, intelligent. No history of syphilis in parents or of deformity in any of patient's relatives. Small child. Head shows remarkable projection upward of anterior part of cranium, and marked bulgings in temporal regions. Face broad and flat. Eyes very prominent and widely separated. Nose small, bridge short and narrow. Head, 48.5 cm. in circumference; anteroposterior diameter, 15.6 cm.; bitemporal, 14.2 cm.; height of face, chin to hair, 14.5 cm. Cranial index, 91.7. Most remarkable features of measurements are great excess in height and width. Forehead very high and vertical in middle line. Distinct depression above outer part of superciliary ridge. Face slightly asymmetrical. Superior maxillae poorly developed. Mouth kept open. Palate narrow, very highly arched; premaxillae deficient. "On both sides, on extension and supination, of forearm, the head of the radius becomes sublaxated forward, apparently owing to laxity of ligaments. On flexion the head of the bone returns into place." "But in this case it appears probable that the slight defect is congenital, as it is symmetrical and associated with developmental defects in other parts of the body." Phalanges of great toes abnormally broad. Slight hallux varus. Interphalangeal joints ankylosed with some inversion Arches of feet flat. Knee-joints rather large. Slight genuvalgum. (Photographs of front and side of head; no roentgenograms.)

CASE 22.—Hutchinson,[92] 1910. Girl, age 1 year, first child. Full term; at time of birth mother aged 25 years. Oxycephalic-shaped head; circumference, 16.5 inches. Suture between frontal bones open to root of nose; coronal and sagittal sutures closed. Eyes wide apart, divergent; slight nystagmus, both rotary and lateral; "disks pale, atrophic." Hands show webbing between ring and middle fingers on left side, and to less degree on right; phalanges normal. Toes rather irregularly arranged. Some evidence of adenoids. Viscera healthy. Mental condition doubtful. (Description fragmentary; photograph of front view of head; no roentgenograms.)

CASE 23.—Hutchison, 1910. Girl, aged 5 years. Youngest of seven; others normal; two died in infancy. Three miscarriages; one monster with "head like a cow." Full term; always healthy. Oxycephalic head with flat occiput and ridge up middle of forehead. Exophthalmus; eyes directed outward; pupils eccentric, upward and inward. Right responds well to light, left sluggish; disks atrophic, sight defective; adenoid facies; high arched palate. "Hands show short (bifid) thumbs, only two phalanges in left index; one long and a short terminal. Toes webbed, and great toes very short." Impossible completely to extend elbows. Viscera normal. Mental condition normal. (Description fragmentary; photograph of front view of head; no roentgenograms.)

CASE 24.—Cameron,[28] 1918. Baby (sex not stated), 8 weeks old. One other child in family healthy. No affection similar to patient's appears in family history. Deformities present at birth. Skull shows "the ordinary appearance of mild oxycephaly." Eyes prominent. Eye grounds normal. Symmetrical deformity of extremities which consists apparently in "giant great toes and giant thumbs consisting of the union of two separate thumbs and two separate toes." (Inadequate description; no photographs; no roentgenograms. The author states he has seen one other case exactly similar to the one described.)

III. CASES OF ACROBRACHYCEPHALY WITH DEFORMITIES OF EXTREMITIES PROBABLY OF THE SAME GENERAL NATURE AS THOSE IN OTHER CASES, BUT UNPROVEN

(Cases 25 to 28, inclusive.)

CASE 25.—Donaldson,[26] 1903. Boy, aged 2½ years. Proptosis so extreme that right eye had become dislocated on eleven different occasions. Upper part of forehead keel-shaped. Brachy and acrocephaly. "The great toes were broad and hallux varus was present on each side."

Case 26.—Fletcher,[34] 1910. Boy, 14 years old. Oxycephalic skull. Exophthalmus and divergent squint. Superior maxilla shortened. Ear poorly developed, tragus rudimentary. Peculiar malformation of thumbs; first phalanx curved outward toward the radial side, the outward or radial side being shorter than the inner. (Report brief; photographs of hands and of front and lateral views of head; roentgenogram of head.)

Case 27.—Hutchinson,[92] 1910. Girl, aged 4 years; ninth of ten children. Full term; rather difficult labor; mother had severe fright at sixth week of pregnancy. Oxycephalic head; circumference 17.5 inches. Exophthalmus with divergent eyes, left turned slightly down and out. Constant, irregular, chiefly lateral movements. Pupils react sluggishly to light; disks show well marked atrophy of secondary type with white lines along course of vessels; vision much impaired. Adenoid facies; high palate; narrow naso-pharynx; tubercle of atlas very prominent. Thumbs very broad; little fingers kinked like those of a Mongol. Viscera normal. Mental development backward. (Photograph of front view of head and hands shown: in Fletcher's report, Plate 36, photographs of front and lateral views of head of this case when 12 years of age are shown; also roentgenogram of head.)

Case 28.—Fletcher, 1910. Man, aged 23 years. Head typically oxycephalic. Extreme proptosis; right eye more prominent than left; occasionally becoming dislocated forward in front of eyelids. Superior maxilla shortened from before backward. Hard palate, narrow, much arched. Elbows cannot be fully extended. Internal condyles unduly prominent. Some creaking in joints; head of both radius and ulna appears thickened. Unable to raise arms to horizontal; obvious creaking in both shoulder joints but no change found in the bones. (Well described; photographs of hands and arms, front and lateral views of head; roentgenograms of head and elbows.)

IV. CASES OF SCAPHOCEPHALY WITH SYMMETRICALLY DISTRIBUTED MALFORMATIONS OF THE EXTREMITIES

(Cases 29 and 30.)

Case 29.—Küttner,[98] 1913. Boy, aged 1 year 2 months. Deformity of head fully developed at birth. Forehead extremely high and rises sheer; head very long. Region of anterior fontanel especially prominent; both fontanels appear to be closed. Sutures cannot be felt. Veins of scalp prominent. Root of nose depressed. Extreme degree of exophthalmos; eyeballs only partially covered by lids; optic neuritis present. Beneath occipital prominence a small flat "prolapse of brain" which pulsates and can be compressed. Extremities show "slight deformities of both thumbs and great toes." Marked convolutional atrophy shown in roentgenogram. Necropsy showed well marked internal hydrocephalus. (Description fair; photographs of head; roentgenogram of head; necropsy.)

Case 30.—Authors. W. F.; first child, labor difficult, delivery instrumental. Child thought to be dead at birth. Deformity fully developed at birth. When seen at 4 months, head extremely high and long; parietal bones form a rounded arch; head acroscaphocephalic. Anterior fontanel very large, measuring 9.5 cm. in breadth by 10 cm. in length, tense and bulging. Posterior fontanel open, measuring 4.75 cm. by 0.5 cm. Wormian bone in anterior fontanel. Veins of scalp prominent. Mouth kept open; nasal obstruction. Marked proptosis. Palpebral apertures slant slightly outward and downward. Internal hydrocephalus of communicating type demonstrated by phenolsulphonephthalein test. Rudimentary tail present. Arms could not be completely extended at elbows. When seen at 3½ years, deformity of head and exophthalmos even more striking. Fontanels closed; marked bony prominence at the site of anterior fontanel. Child apparently sees and hears but is mentally retarded.

THE CALCIUM METABOLISM OF PREMATURE INFANTS *

BENGT HAMILTON
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The calcium metabolism of premature infants has hitherto not been studied systematically. Such a study is, however, well justified by the fact that these infants are more liable to acquire rachitis than full-term babies. It is also a common experience that bone symptoms appear in the prematurely born at an early age, and that the condition more often takes a grave course than in other infants. It has been assumed that this tendency is caused by the absence of a congenital store of calcium, supposed to be present in full-term new-borns. About 85 per cent. of the body's calcium at birth is stored during the last two or three months of fetal life.[1] We do not know, however whether the large amount of calcium, thus retained, may in postnatal life really play the rôle of a depôt, the contents of which are available for the processes of growth. Be this as it may, a premature birth means that the body is exposed to postnatal life containing a proportionately very small amount of calcium. It has been surmised that this fact may be at least partially responsible for the prevalence of rachitis among the prematures.

If the calcium stored in the last months of fetal life, really is essential to the normal postnatal growth of the body, the premature birth would, it seems, lead to a state of calcium starvation. According to the present state of knowledge, however, rachitis and calcium starvation are not identical conditions. It might be possible that the assumed calcium starvation of the prematures would in some way make them more susceptible to rachitis. But there is also another possibility, namely, that some of the so-called rachitic symptoms of the prematures have nothing to do with rachitis, but are symptoms of simple osteoporosis.

One peculiarity of rachitis in prematures is the very early appearance of craniotabes. This symptom, rarely seen in full-term infants before the beginning of the fourth month, very often appears in prematures as early as the second month of life. (The craniotabes in prematures must not be confused with the general elastic flexibility of the flat bones of the skull in these infants; nor, of course, with con-

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* From the "Sachs" Baby Hospital.

* Read in part before the First Scandinavian Pediatric Congress, Copenhagen, August, 1919.

1. Schloss: Die Pathogenese und Aetiologie der Rachitis sowie die Grundlagen ihrer Therapie, Ergebn. d. inn. Med. u. Kinderh. **15**:55, 1917.

genital bone defects). This early craniotabes of the prematures often develops to an extent rarely seen in infants born at full term. It is noteworthy that this excessive softening of the flat bones of the skull is often found in breastfed prematures in the best hygienic conditions, spared from infections and gaining rapidly in weight. The general condition of these infants, their often remarkable vitality, makes one doubt whether they are suffering from a rather severe disease; clinical observation as well as theoretical speculation therefore justifies the assumption of a nonrachitic origin of their symptoms in many cases.

The predisposition of prematures to acquire rachitis, however, can hardly be denied altogether. Among the cases of malignant rachitis in older infants, the cases with severe deformities of thorax and extremities, with general slackness of the muscles, there is a large percentage of prematures according to the experience gathered at this hospital.

TABLE 1.—Summary of the Main Results of Previous Works on Calcium Metabolism of Breast-Fed Infants

Author	Age in Mos.	Weight	Calcium Oxid			
			Total Intake	Intake per Kg.	Total Retention	Retention per Kg.,
Peiser, Gl*............	2	3,720	0.279	0.075	0.048	0.013
Tobler-Noll†...........	2.5	4,000	0.2390	0.0598	0.0533	0.0133
Lindberg I‡............	2.5	4,285	0.2572	0.0600	0.0562	0.0131
Lindberg II............	2.5	4,370	0.2615	0.0598	0.0639	0.0146
Michel Perret§.........	3	4,725	0.377	0.080	0.149	0.032
Schabad¶..............	4	7,700	0.3636	0.0472	0.1815	0.0236
Blauberg#..............	5	6,740	0.272	0.0404	0.1754	0.0260
Howland and Stolte I‖	5	About 4,250	0.3337	0.0785	0.1053	0.0248
Howland and Stolte II	6	About 4,400	0.3307	0.0752	0.1107	0.0252

* Peiser: Beiträge zur Kenntnis des Stoffwechsels, besonders der Mineralien im Säuglingsalter, Jahrb. f. Kinderh. **81**: 437, 1915.

† Tobler and Noll: Zur kenntnis des Mineralstoffwechsels beim gesunden Brustkind, Monatschr. f. Kinderh. **9**: 210, 1910.

‡ Lingberg: Ueber den Stoffwechsel des gesunden, natürlich ernährten Säuglings und dessen Beeinflussung durch Frauenmilchfett, Ztschr. f. Kinderh. **16**: 90, 1917.

§ Michel and Perret: Etude des échanges nutritifs azotés et mineraux chez un nourrison, Bull. Soc. d'obstét. de Par. 1899.

¶ Schabad: Zur Bedeutung des Kalkes in der Pathologie der Rachitis, Arch. f. Kinderh. **52**: 47, **53**: 380, **54**: 83, 1910.

# Blauberg: Ueber den Mineralstoffwechsel beim natürlich ernährten Säugling, Ztschr. f. Biol. **40**: 36, 1900.

‖ Howland and Stolte: Die Bedeutung von Eiweisszulagen beim Säugling, Jahrb. f. Kinderh. **88**: 85, 1918.

The proportionately small amount of calcium in the body of the new-born premature may, as mentioned above, possibly lead to a state of calcium starvation in the course of postnatal growth. There are, however, in the postnatal growth of the premature often certain characteristic features which also might unfavorably influence the calcium metabolism. Although the difference in corporal development between the premature and the full term new-born may be very great, there is in the healthy premature, when properly nourished and cared for, a great tendency to make good this difference. It is not unusual for such an infant to double its weight in three months and triple it in six months. The question now arises, whether the tissues formed by this rapid growth are of the same composition as in the more slowly growing bodies of normal infants. We know how the tissues formed in a rapid recovery from an acute or chronic nutritional disturbance, contain much water and are poor in salts. It may well be supposed that the same would be the case in the rapidly growing bodies of prematures. If this should be so, their bodies, already containing but a small amount of calcium at birth, would soon be really impoverished in respect to this substance.

The work of Klotz has been excluded, first because the infant practically did not gain in weight, and second because the calcium intake was abnormally low. One of Peiser's infants (infant Band) has also been excluded. This infant developed symptoms of syphilis some time after its metabolism had been studied and cannot, therefore, be considered a normal infant.

A study was made of infants born from four to ten weeks before full term. The cause of the premature birth was advanced pulmonary tuberculosis of the mother in three cases, nephritis and eclampsia in one case. In the cases of tuberculosis, the infants were separated from the mothers immediately after delivery. Symptoms of syphilis and tuberculosis were absent in all cases during the time of observation. The Wassermann test was negative. The infants were nourished from birth exclusively with breast milk given in bottles; they gained rapidly in weight during the months in which the experiments were carried out. A slight tendency to subnormal temperature was easily overcome. The stools were at times loose and frequent, both during the experiments and in the intervals. Such stools are often seen in normal babies fed with breast milk, and are nowadays not considered pathologic when, as in these cases, the infants are in all respects healthy, gaining in weight and showing a normal temperature.

The method used for collecting the stools and the urine was that described by Bendix-Finkelstein, slightly modified. Calcium was determined according to McCrudden.

The iron metabolism of these same infants was studied by Lichtenstein as a sequel to hematologic studies made on prematures.[2] The result of this study has not yet been published.

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[2] Lichtenstein: Hämatologiska studier å för tidigt födda barn, Svenska Läk.-Sällsk. Handl. **43**:1533, 1917 (abstr. in Jahrb. f. Kinderh. **88**:387, 1918.

TABLE 2.—STUDY OF THE CALCIUM METABOLISM OF FOUR PREMATURELY BORN INFANTS

Case	Date and Number of Experiment	Weight at Beginning and End of Experiment	CaO Intake, Gm. Daily	CaO Intake, per Kg., Gm. Daily	CaO in Feces, Gm. Daily	CaO in Urine, Gm. Daily	CaO, Total Output, Gm. Daily	Total Retention, Gm. Daily	Retention per Kg. Gm. Daily	Percentage of Intake Retained	Remarks
A. L. Born 11/18	12/10-12/19 I	1,930—2,140	0.1444	0.0710	0.0997	0.0107	0.1103	0.0340	0.0167	23.6	
	1/20- 1/29 II	2,830—3,150	0.2448	0.0819	0.2013	0.0051	0.2064	0.0384	0.0128	15.7	1/2: craniotabes
	3/20- 3/29 III	4,170—4,390	0.3097	0.0724	0.2041	0.0074	0.2115	0.0982	0.0229	34.7	3/6: extensive craniotabes
N. L. Born 11/30	1/ 3- 1/12 I	1,620—1,760	0.1339	0.0792	0.1130	0.0057	0.1187	0.0152	0.0090	11.4	1/13: craniotabes
	2/22- 3/ 3 II	2,620—2,870	0.1876	0.0683	0.1719	0.0076	0.1796	0.0081	0.0030	4.3	2/20: extensive craniotabes
	4/ 2- 4/ 6 III	3,670—3,840	0.2695	0.0718	0.2000	0.0080	0.2080	0.0615	0.0164	22.8	4/4: craniotabes progressing (the hole back of the skull)
	4/ 7- 4/ 9 IIIa	3,840—3,970	0.2976	0.0762	0.2239	0.0106	0.2345	0.0635	0.0165	21.3	Milk, 4/7-5/1, slightly enriched in calcium through addition of $CaCl_2$
	4/25- 5/ 1 IV	4,250—4,420	0.3092	0.0713	0.2024	0.0160	0.2184	0.0988	0.0228	29.4	5/27: extensive craniotabes; osteophytes on tubera frontal; slight rosary
S. P. Born 1/15	2/10- 2/19 I	1,770—1,970	0.1362	0.0728	0.1300	0.0054	0.1354	0.0008	0.0004	0.6	
	3/ 5- 3/14 II	2,210—2,440	0.1786	0.0768	0.1601	0.0053	0.1654	0.0132	0.0057	7.4	3/4: craniotabes; 4/3: craniotabes progressing
O. Born 5/17	6/ 6- 6/15 I	1,850—2,100	0.1637	0.0829	0.1490	0.0107	0.1597	0.0040	0.0020	2.4	
	6/17- 6/18 Ia	2,110—2,170	0.2789	0.1303	0.2075	0.0146	0.2221	0.0568	0.0265	20.4	Milk, 6/16-7/5, slightly enriched in calcium through addition of $CaCl_2$
	6/26- 7/ 5 II	2,290—2,560	0.2823	0.1164	0.2116	0.0193	0.2309	0.0514	0.0212	18.2	
	7/11- 7/20 III	2,690—3,020	0.2350	0.0823	0.1659	0.0031	0.1690	0.0660	0.0231	28.1	7/21: craniotabes

REPORT OF CASES

CASE 1.—A. L., born Nov. 18, 1918, four weeks before full term, with a birth weight of 1,930 gm. Admitted to the "Sachs" Baby Hospital November 27.

The calcium metabolism of this infant was studied in the second, third and fifth month (ten day periods). The calcium retentions found per kilogram of body weight were of the same magnitude as those found by other investigators in full term infants. Craniotabes appeared shortly after the end of the first period and progressed rapidly in the following months.

CASE 2.—N. L., born Nov. 30, 1918, from eight to ten weeks before full term. Birth weight, 1,550 gm. Admitted December 13.

The calcium retentions found in the second and third months (two ten day periods) were very low. Craniotabes appeared in the second month and progressed rapidly, until in the fourth month the whole back of the skull was softened. Somewhat later there also developed osteophytes on the frontal bones and rosary. At this time a five day period showed a tolerable calcium retention. Calcium chlorid was now added to the milk (about 0.03 gm. daily); the retention remained the same (period III a, three days). The administration of calcium chlorid was continued, and two weeks afterward the retention was decidedly better (period IV, seven days), whether because of the artificially increased intake it is impossible to decide.

This infant spent thirty-five days out of 124 on the metabolism frame. The calcium retention was never found to be negative, although pronounced pathologic bone symptoms appeared and progressed during this time.

CASE 3.—S. P., born Jan. 15, 1919, from six to eight weeks before full term with a birth weight of 1,600 gm. Admitted January 17.

The calcium metabolism was studied in the first and second month of life (ten day periods). The retentions were very low. Craniotabes appeared in the second month.

CASE 4.—O., born May 17, 1919, one month before full term. Birth weight 1,670 gm. Admitted May 24.

The first experiment with this infant was made when it was 3 weeks old (a ten day period). The calcium retention was found to be very low (0.0020 gm. per kilogram). When this period was finished, calcium chlorid was added to the milk (about 0.1 gm. daily). Twenty-four hours afterward a second period (I a, two days) was begun. The retention was now more than tenfold (0.0265 gm. per kilogram). The administration of calcium chlorid was continued. Eight days after the second period a third period (II, ten days) showed about the same retention (0.0212 gm. per kilogram). Calcium chlorid was now left out. In spite of this, the retention found in the last period was not altered; a fact, the probable explanation of which will appear from the discussion of the experiments. Craniotabes appeared in this infant shortly after the end of the experiments.

DISCUSSION

Three infants out of four studied had very low calcium retentions during the first months of life. This might possibly be ascribed to rachitis, as in all the infants craniotabes appeared in the second month. This assumption, however, is not in harmony with the fact that although the craniotabes in those cases which were followed further made progress in the subsequent months, the retentions increased to amounts as large as those found in normal infants. I wish further to call attention to the relatively normal retention of the infant A. L., period I, immediately before the craniotabes was clinically noted; the appearance of rachitic symptoms is generally believed to be preceded by low or negative calcium retentions. Lastly, the calcium metabolism in progressive rachitis cannot, as far as we know, be influenced by the administration of calcium, as was done in the case of the infant O.

There are, then, several discrepancies between these prematures and rachitic infants in respect to their calcium metabolism, its relations to clinical symptoms and therapeutic measures—discrepancies which justify the proposal of another explanation of their low retentions.

TABLE 3.—Total Intakes Compared with the Retentions Per Kilogram of Body Weight

Case	Period	Total Intake in Mg.	Retention per Kg. of Bodyweight	Case	Period	Total Intake in Mg.	Retention per Kg. of odyweight
N. L.	I	133.9	9.0	A. L.	II	244.8	12.8
S. P.	I	136.2	0.4	N. L.	III	269.5	16.4
A. L.	I	144.4	16.7	O.	Ia	278.9	26.5
O.	I	163.7	2.0	O.	II	282.3	21.2
S. P.	II	178.6	5.7	N. L.	IIIa	297.6	16.5
N. L.	II	187.6	3.0	N. L.	IV	309.2	22.8
O.	III	235.0	23.1	A. L.	III	309.7	22.9

In Table 3 the rather remarkable fact is demonstrated that in those periods where the intakes exceed 200 mg., the retentions are sufficient (i. e., as large as in normal infants), while in the periods where the intakes are lower than this amount, there is sufficient retention only in one case. It is tempting to draw the conclusion that the intake must exceed a minimum of about 200 mg. if sufficient retentions are to be attained. The total calcium excretion cannot, it seems, be pressed below a certain level. The calcium is excreted mainly in the stools. The daily amount of feces excreted by prematures is very large, a fact which may be explained by the low fat absorption found in prematures by Rubner and Langstein. The daily values for the total solids [3] in the stools are consequently high, higher than in normal infants, although the quantities of milk taken by the prematures are very small. The calcium percentages of the total solids were, in my experiments, found to be lower than in normal infants, not, however, sufficiently lowered to counterbalance the excess in total solids and the small intakes. To balance these factors, exceedingly low calcium percentages would have been necessary. It might be conceivable that for reasons unknown to us, such exceedingly low percentages cannot be attained under ordinary conditions.

Lindberg's experiment [4] where an infant was alternately fed with ordinary breast milk and breast milk enriched with fat (breast milk fat used), demonstrates that a high fat intake may in the breast fed infant lead to temporary losses of calcium. The increased fat intake was followed by an increased fat excretion, i. e., an increase of the daily amount of total solids in the stools; the dry weight of the stools increased 27 per cent. The calcium percentage, however, fell only 15 per cent., i. e., the increase in total solids was not balanced. Lindberg's experiment with high fat intake lasted only six days. During this time, the feces had the same characteristics as the feces of prematures: rich in fat and consequently in total solids; calcium percentage somewhat low, but not sufficiently lowered to bring about a good calcium retention. In the normal infant the cause was an excess of fat intake; if the experiment had been continued for a longer period, it is highly probable that some regulating mechanism would have been called into play and a normal calcium metabolism re-established. In the premature, the constantly low fat absorption suggests an insufficiency of the digestive mechanism. It is not inconceivable that this supposed insufficiency is also responsible for the low calcium retentions.

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[3] As fat analyses have not been made (because of lack of the necessary reagents) the following discussion is based on the values for total solids.

[4] Loc. cit., Table 1.

Holt and his co-workers[5] in their work on calcium and fat metabolism in bottle fed infants found no constant relation between calcium and fat excretion. The work of Lindberg demonstrates that in a breast fed infant with abnormally high fat intake such a relation may exist. Perhaps the experiments here reported may be interpreted thus: that in breast fed infants the same relation is found when the fat absorption is low.

In this discussion, an attempt has been made to find a plausible nonrachitic cause for the low calcium retention found in prematures. The argument would be strengthened if it could be demonstrated that these low retentions may be increased not only by a higher calcium intake but also by a lower fat intake.[6] At present, however, the available facts are neither numerous nor complete enough to justify the drawing of definite conclusions.

I wish to thank Dr. A. Lichtenstein for taking the initiative in this work, and for his valuable advice and criticism.

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[5] Holt, Courtney and Fales: Calcium Metabolism of Infants and Young Children, and the Relation of Calcium to Fat Excretion in the Stools, Am. J. Dis. Child. **19**:97 (Feb.) 1920.

[6] In the discussion of this paper Dr. A. Ylppö announced that he had recently begun feeding prematures with centrifugated breast milk. The result of this experiment has not yet been published.

OBSERVATIONS ON TUMORS OF THE KIDNEY REGION IN CHILDREN*

LANGLEY PORTER AND WILLIAM E. CARTER
SAN FRANCISCO

Tumors in the kidney region of children may be either benign or malignant. Cystic enlargements of the kidneys are fairly common. The benign growths may appear as adenomas, angiomas, lipomas or fibromas. Cysts occur as congenital cystic kidney; acquired as results of hydronephrosis or of pyonephrosis, or as hydatid cysts. Reports of cases of congenital hydronephrosis without malignancy are included in this study.

Malignant tumors of the kidney are grouped variously. An accepted classification has yet to be made. In general, these cases fall into the group of carcinomas, sarcomas and hypernephromas.

The malignant tumors of the kidney region are the kind which usually occur in young patients. The greatest number of cases occur between the ages of 6 months and 6 years. Of all malignant growths affecting children, those affecting the kidneys appear to be second in number. D'Espine and Piso constructed a table which sets forth in order of frequency the structures involved in cases of malignant tumors occurring in children. Three hundred and ninety-three cases were analyzed. The eye and orbital structures were involved in 52 per cent.; the kidney in 20 per cent.; the bone in 17 per cent.; the brain in 5 per cent. and the abdomen and pelvis in 4 per cent.

Albarran and Imbert tabulated 600 cases of kidney tumors occurring at all ages. Twenty-two of these were in children. Forty per cent. were epitheliomas; 20 per cent. were hypernephromas, and 30 per cent. were mixed tumors. Other writers have reported equally significant figures.

In looking over the case records of the University of California Hospital, Stanford University Hospital, San Francisco Children's Hospital and our own case records for the last five years, we have been able to find eleven cases. They fall into the following groups: Sarcoma, 4 cases; carcinoma, 3 cases; malignant kidney, unclassified, 2 cases, and hydronephrosis, 2 cases.

All the patients were less than 7 years of age.

Sarcomas have been found in the kidney as early as the sixth month of fetal life. Many references are made in the literature to two cases reported by Paul of Liverpool in which the tumor was discovered during the examination of the kidneys of stillborn infants. It is probable that more cases would be reported if routine histologic examination of stillborn babies were the rule.

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One case coming under our observation was of unusual interest. The tumor was found in a child at term. The mass was so large that it obstructed labor. While the literature contains several reports of cases of small malignant kidney growths found at birth, we have been unable to find any reference to the antenatal development of a tumor of such dimensions.

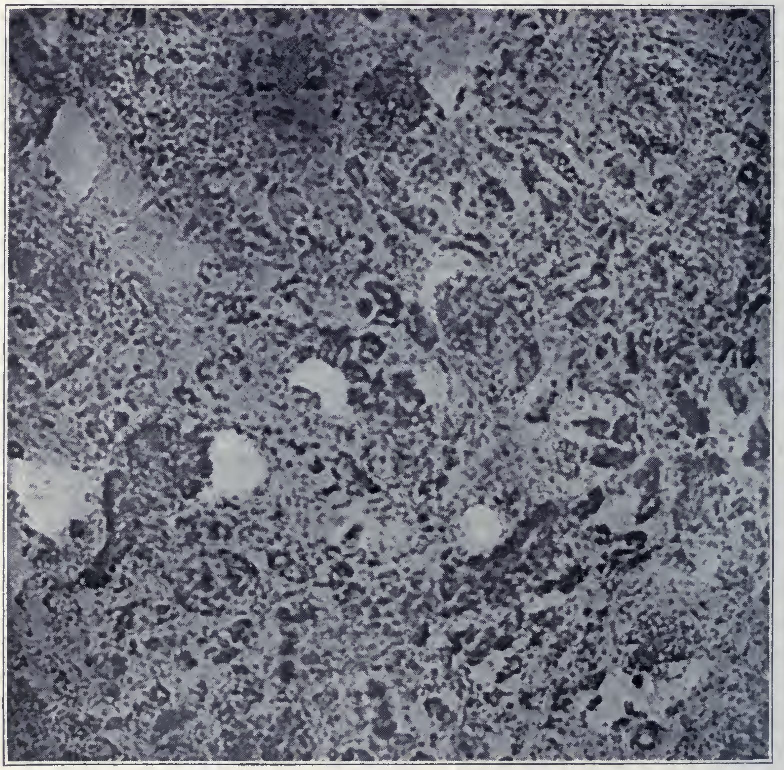

Fig. 1.—Microscopic section of round cell sarcoma of kidney.

REPORT OF CASE

Mrs. P., aged 35; Italian; first baby at 16 years. Has had five pregnancies, four with normal course and delivery. Of these children, one died at 4 years of appendicitis; three are living and well.

There is a history of a severe and protracted cold, extending over the first four months of pregnancy. Emesis occurred daily from the fourth to the sixth month. Other than these two features, there was nothing unusual in the course.

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1. Called to our attention by Dr. A. S. Musante and Dr. Thomas Maher.

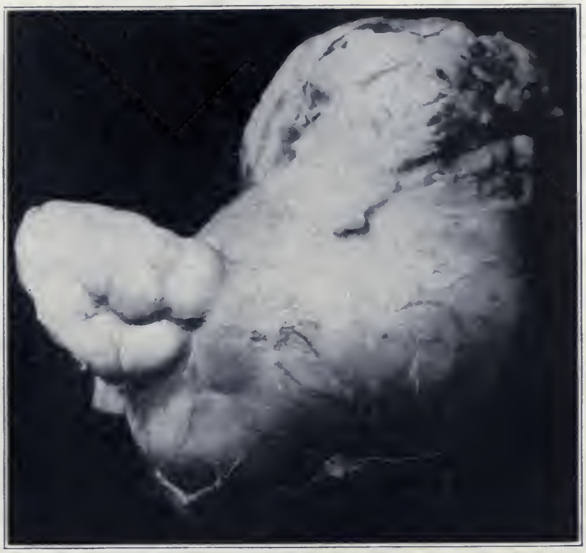

Fig. 2.—Sarcoma of kidney.

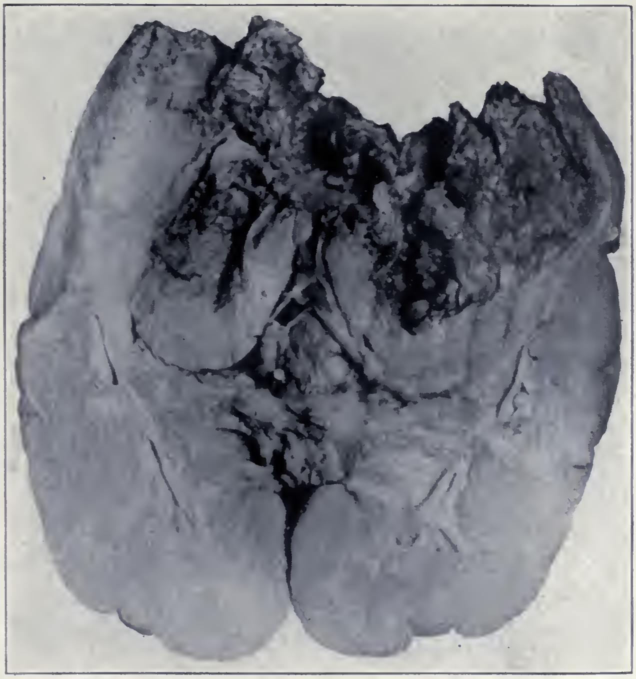

Fig. 3.—Carcinoma of kidney; cross section.

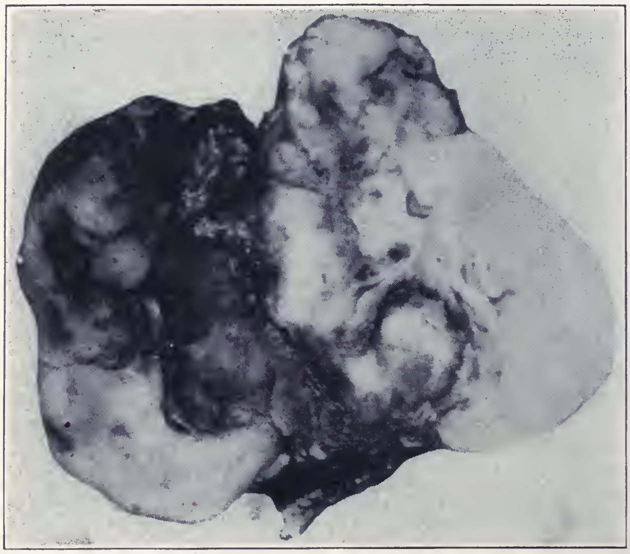

Fig. 4.—Carcinoma of kidney; cross section.

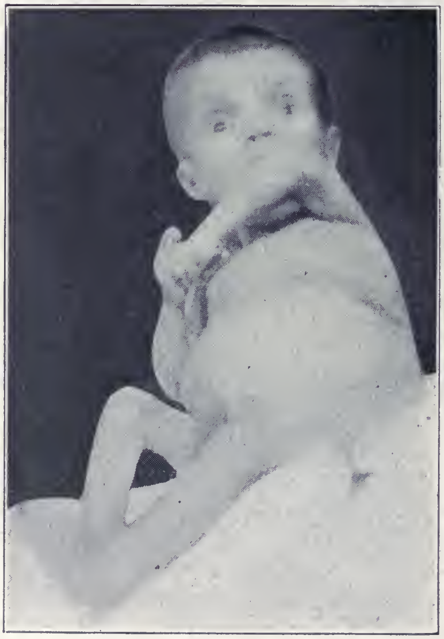

Fig. 5.—Case of hydronephrosis, result of congenital narrowing of ureter; authors' case.

Labor: Beginning at 5 p. m., the patient had pain in her back and lower abdomen. At 9 p. m. she had a sudden rupture of the membranes with a discharge of black fluid. At 11 p. m. the head, shoulders and arms of the child were delivered, but the remainder of the body could not be brought down. The attending physician called a consultant. The patient was anesthetized; an incision was made in the body of the dead fetus just below the ensiform cartilage; the hand was introduced and a large amount of soft, friable tissue was removed from the abdominal cavity of the infant. This manipulation reduced the tumor mass sufficiently for the body to pass through the birth canal.

In size the mass appeared to be one and a half to two times that of the fetal head. The part of the tumor which was removed was of grayish color; a pinkish framework ran through it and it was semisolid in consistency.

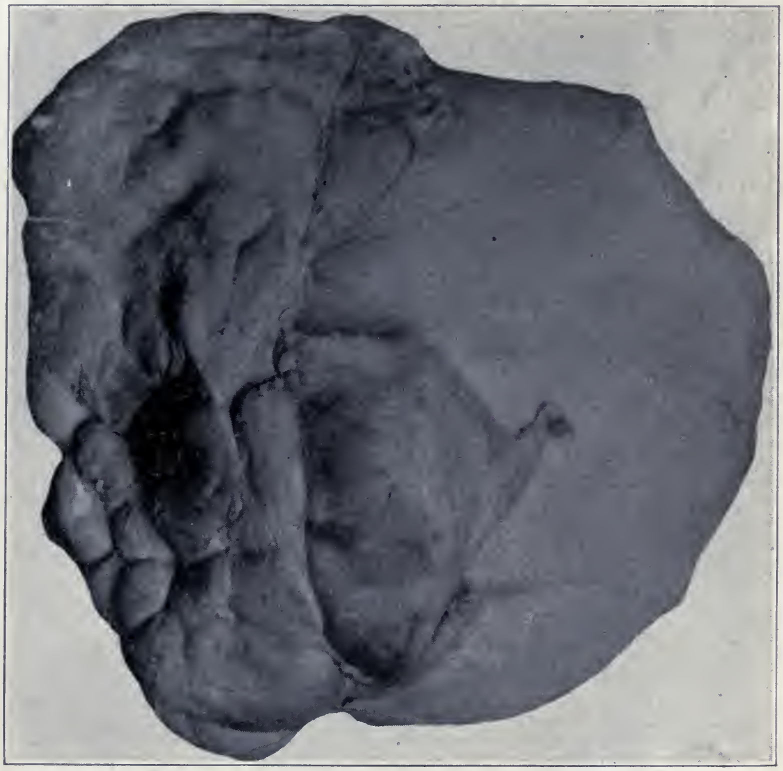

Fig. 6.—Kidney from authors' case.

The pathologist's report showed the tissue to be a round-cell sarcoma. The presence of glomeruli in the section indicates the kidney origin of the tumor (Fig. 1).

DISCUSSION OF CLINICAL HISTORY AND OF THIS TYPE OF CASE

True sarcomas are usually irregular in form, and they are contained within the fibrous capsule of the kidney. Their color varies from that of the meat of a white fish to a bright red. They may attain great size; one reporter saw removed from a child a kidney tumor which weighed more than the postoperative weight of the

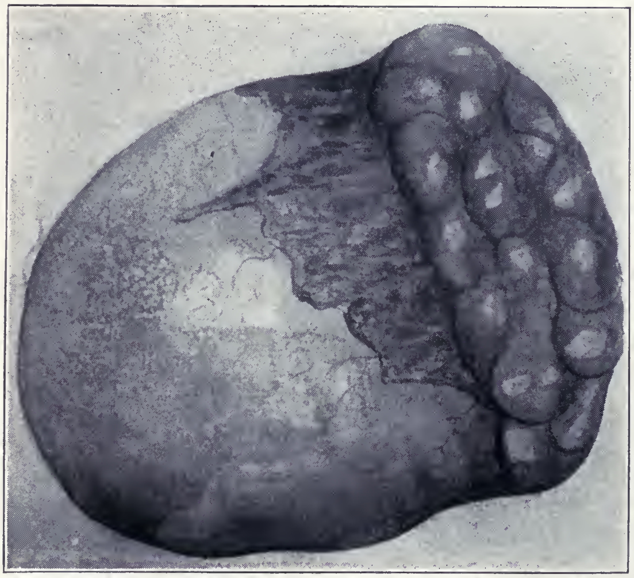

Fig. 7.—Another view of kidney from authors' case.

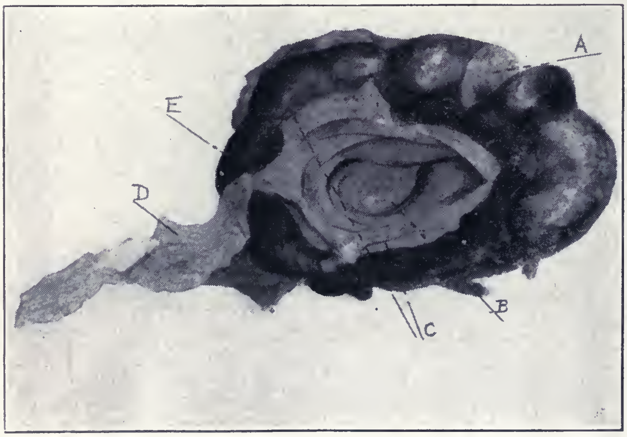

Fig. 8.—Photomicrograph of a malignant kidney producing dystocia?

patient from whom it was taken. Several cases are reported in which the tumor is said to have weighed from ⅓ to ½ of the child's post-operative weight. On cut section, these tumors exhibit any degree of hardness, from woody to scirrhus. Occasionally there will be found scattered throughout the kidney structure cysts which represent late hemorrhages or mucinous degeneration. Such cysts may lead to errors in diagnosis as the fluctuation may be mistaken for that of a true cyst or a hydronephrosis. Metastases sometimes occur in the lymph nodes, liver, peritoneum, pancreas and bladder.

The symptoms and signs of malignancy of the kidney are fairly uniform, and the diagnosis can usually be made before the child is cachectic. Early in the course there is commonly a period of anorexia, malaise and vomiting. The loss of weight is progressive. Pain is frequently an early symptom. The temperature ranges from normal or subnormal during the early stages to 104 or 105 F. during the later days.

The physical signs consist of the early appearance of a fullness at the costo-vertebral angle of the affected side. Later, a tumor mass may be revealed by palpation and percussion. In many cases, this mass fills a large part of the abdomen. Ballottement, gently applied at the costo-vertebral space, is of paramount importance as a diagnostic measure. The firm but gentle, intermittent pressure of the finger applied here, usually senses enlargements in the kidney or about it.

If the urine is watched, it will be found that intermittent hematuria is not infrequent. Pus cells and casts are often found. The blood changes are seldom more than those of a secondary anemia.

A roentgenogram is of particular value in arriving at a diagnosis. A good anterior projection will occasionally show the tumor mass clearly outlined. Injecting the colon with oxygen or air will often assist in defining the shadow of the tumor. The more recent advances in roentgenography in which oxygen or carbon dioxid is injected into the peritoneal cavity may prove to be of considerable value.

Renal malignancy may be mistaken for a tuberculous peritonitis, but in the latter condition there is usually felt a sausage-shaped mass extending diagonally across the abdomen. This tumefaction corresponds to the free margain of the mesentery. Fullness at the costo-vertebral angle, so characteristic of kidney tumor, is rarely found in tuberculous peritonitis.

The disease runs a rapid course. Guillet says that children so affected die on an average within a year. Roberts and Taylor say seven months. Albarran and Imbert state that of twenty children who were not operated on, fourteen were dead within six months after the discovery of the tumor and only one child survived three years (Figs. 2, 3 and 4).

Malignant kidney tumors may be confounded with hydronephrotic. The diagnosis is especially difficult when such a tumor degenerates, acquires fluid and on physical examination is found to fluctuate.

Hydronephrosis, Figures 5, 6, 7, 8, is produced by obstruction of the ureters and a damming back of the urine. This obstruction may be due to pressure from without or to a stenosis or an atresia of the ureter. A solid tumor of the kidney, by virtue of its size, may press on the ureter of the opposite kidney and so give rise to a hydronephrosis. Pressure on a ureter from impingement of an anomalous accessory renal artery may lead to retention of urine in the kidney. Occasionally a concretion lodged in the kidney pelvis or in the ureter may be the cause of the blocking. A congenital narrowing of the ureter may be the etiologic factor, as in one of our cases (Fig. 8).

SUMMARY

1. Malignant kidney tumors may develop in the child in utero and become of sufficient size to obstruct labor.

2. Ballottement, applied to the costo-vertebral space, is of value in the diagnosis of tumors in the kidney region, and this maneuver should be routinely employed in the examination of children.

STUDIES IN METABOLISM. II. THE METABOLISM OF A VERY OBESE CHILD WITH A SMALL SELLA TURCICA (TYPUS FRÖLICH ?)

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A boy, W. N., aged 2 years and 9 months, entered the Children's Medical Service at the Massachusetts General Hospital June 9, 1919. He was a full term baby, and for the first nine months was fed on drawn breast milk because his mouth would not open wide enough to permit him to nurse. Up to the end of the first year he was a very thin and poorly developed infant. He then commenced to gain rapidly in weight and has continued to do so up to the present time. His weight on entering the hospital was 24.82 kilos, (54 pounds, 9½ ounces). His mental development was that of a 10 months old infant. He recognized his family, but did not talk or feed himself, and was unable to stand alone. He was said to sleep well, to be happy and contented, and to have a good digestion.

The physical examination showed an extremely obese child with a sluggish mentality and a hoarse voice. His skin was like satin and the hair slightly coarse. The features and all parts of the body were large, except the penis and testicles, which were smaller than normal. There were great rolls of fat all over the body. The physical examination was otherwise normal. His body measurements were as follows:

Naked body weight	24.82	kilos	54 lbs. 9½ ozs.
Height	94	cm.	36⅞ inches
Circumference of head	49.4	cm.	19⅜ inches
Circumference of chest	75.5	cm.	29⅝ inches
Circumference of abdomen	74.4	cm.	29¼ inches
Circumference of hips	73.0	cm.	28⅝ inches
Length of arm	41.0	cm.	16⅛ inches
Length of leg	46.7	cm.	18¼ inches

Body surface (measured by DuBois formula) = 0.879 square meters.

A two hour pulse, respiration, and temperature chart showed that the pulse and respiration responded to muscular activity in a normal manner. The rectal temperature tended to be slightly elevated, between 99 and 100 F. The patient perspired easily and seemed nervous and fussy. The average daily number of calories in the food for three weeks was 895, on which he gained slightly in weight. The average caloric requirement for his age is about 1,200 calories. When the food was cut down to between 700 and 800 calories he commenced to lose weight.

June 10 the administration of 10 grains of whole pituitary gland daily was commenced and continued for a period of five weeks, during which time he had lost eight pounds and had improved both mentally and physically. The pituitary gland was then omitted for four days and he regained some weight previously lost, but lost it when the pituitary gland was again commenced. Toward the end of his stay in the hospital he was trying to walk and commenced to talk.

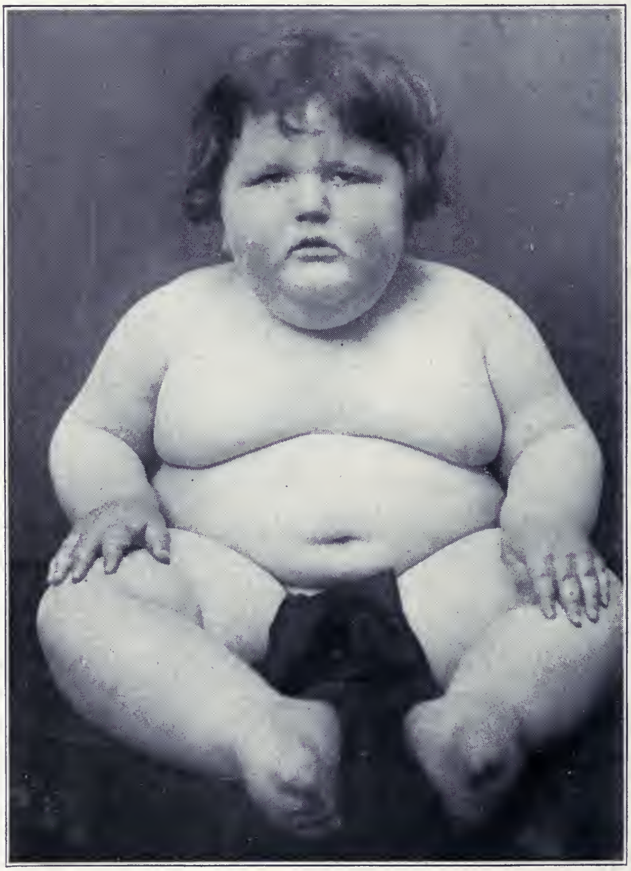

Fig. 1.—Excessive obesity, tapering fingers and stupid facial expression.

A study of the basal metabolism of this child was made in order to determine how much his metabolism varied from the normal found by Benedict and myself.[1] Figures of the basal metabolism represent, of course, the minimum metabolism of a child which is absolutely quiet, without food in the stomach, and in very young children who are usually asleep. These figures are the lowest figures obtainable consistent with life and leave out of consideration the energy required for activity and growth and the energy lost in the excreta. The only way by which comparisons of basal metabolism can be made is when the child is under basal conditions, that is, conditions in which all factors which increase the metabolism above the basal, are excluded.

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[1] Talbot: Metabolism and Growth from Birth to Puberty, to be published later as Carnegie Institution of Washington Publication, No. 302.

His metabolism determined before treatment was commenced was as follows:

TABLE 1.—Metabolism of W. N. Before Treatment

June 9, 1919	CO_2 Produced, Calculated to Hour Basis	Heat Produced per 24 Hours				Average Pulse Rate	Relative Activity
		Total	Per Kilo	Per Sq. Meter			
				Lissauer	DuBois		
	Gm.	Cals.	Cals.	Cals.	Cals.		
Maximum................	....	919	37	1,049	1,046	130	III. Playing with hands and tubing
Minimum................	7.84	626	..	...	...	83	1. Asleep
	8.46	675	..	...	...	80	I. Asleep
	7.46	595	24	679	677	82	I. Asleep
Average minimum.......	....	632	24	679	677	81	I.

His total basal metabolism was found to be the same as that of boys of the same age, that is 631 calories. He was given food containing 895 calories, on which he continued to gain in weight. This would have been surprising if it were not for the fact that he was sitting or lying quietly all day and showed very little desire to move. This left 264 calories in the food which were not used up in the basal metabolism. From this must be subtracted 10 per cent. of the total intake, or, roughly, 90 calories, lost in the excreta, leaving 174 calories to be divided between muscular activity and growth. The gain in weight could only come if the child was very quiet.

When his total metabolism was compared with boys of the same weight, it was found to be 37 per cent. below the average. The heat production per kilogram of body weight when compared to that of boys of the same age was found to be 56 per cent. below the average, and when compared to that of normal boys of the same weight, it was 40 per cent. below the average. This is a very low metabolism and is comparable with that found in J. J. M. previously reported by me.[2]

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[2] Talbot: The Energy Metabolism of an Infant with Congenital Absence of the Cerebral Hemispheres, Arch. Pediat. **32**:452, 1915.

J. J. M. was found to have congenital absence of both cerebral hemispheres and his body was very fat with little muscle. In both of these children the amount of fat, which is inactive so far as the energy metabolism is concerned, was relatively very great as compared to the active tissues such as muscle and organs. The very low metabolism, even when compared to body surface, could, therefore, be due to the obesity of the child.

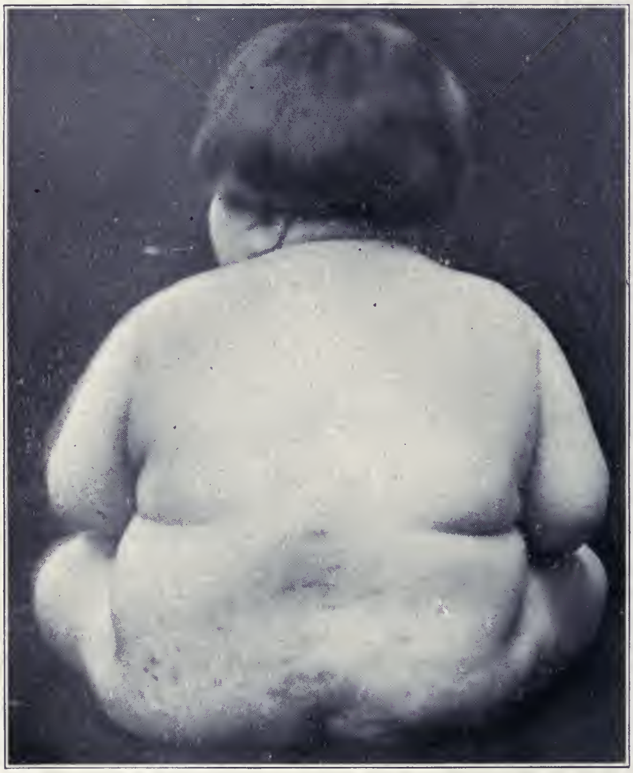

Fig. 2.—Rear view of same patient as shown in Figure 1.

Table 2 sets forth certain points of similarity in three cases. The metabolism per unit of body weight and per square meter of body surface is lower than the average for the same age and sex.

Although the findings in the case of W. N. can be explained in part by the obesity and the absence of muscular tissue, they are out of proportion to what has been found in normal fat children. The question naturally arises whether some other factor may not also play a part in causing the low metabolism.

TABLE 2.—Points of Similarity in Three Cases

Case	Age	Weight	Height	Total Heat			Remarks
				Per 24 Hrs.	Per Kilo	Per Sq. M. Body Surface	
		Kg.	Cm.	Cals.	Cals.	Cals.	
J. J. M.	8 mo.	8.43	73.5	245	27.0	574	Infant without a brain
C. G.	3 yr. 8 mo.	11.83	85.0	479	40.5	898	Cretin [3]
W. N.	2 yr. 9 mo.	24.82	94.0	632	24.0	677	

If the metabolism per square meter of body surface in W. N. is now studied and compared with that of normal boys of his own weight and age, a striking variance from the average will be found. When compared to boys of the same age it is 41 per cent. below normal, and of boys of the same weight, 32 per cent. below normal.

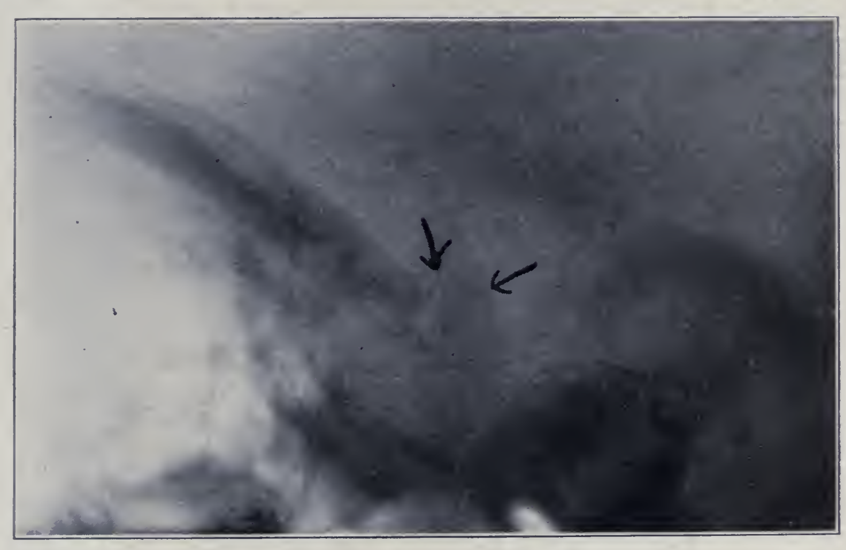

Fig. 3.—Roentgenogram of skull showing constriction of neck of sella turcica and hypertrophy of posterior clinoid process.

Means [4] has shown that simple obesity in adults, as expressed in terms of surface area, does not alter the basal metabolism. In children and infants, on the other hand, there is a tendency for the fatter individuals to have a lower metabolism both per kilo of body weight and per square meter of body surface than for children of the average weight. One might speculate on the importance of observations with such marked deviation from the normal basal metabolism as was found in this case.

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[3] Talbot: Am. J. Dis. Child. **12**:145, 1916.

[4] Means: The Basal Metabolism in Obesity, Arch. Int. Med. **17**:704, 1916.

SUMMARY

W. N. showed a very low metabolism from every point of view as compared with normal children of the same age, except the total basal metabolism. When he did not receive the pituitary extract he gained in weight and presumably put on fat very rapidly even on a diet containing relatively few calories. After pituitary extract was supplied he lost weight and commenced to develop mentally. It is to be hoped that the metabolism of similar cases will be studied in the future and thus throw light on such obscure conditions as this child presents.

THE FATE OF SUBCUTANEOUSLY INJECTED RED BLOOD CELLS *

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PART I.

Modern methods of intravenous transfusion are so satisfactory that today the question of using an extravascular route arises in infants only. A study of the older writings shows that at different times and places both the subcutaneous and intraperitoneal routes were employed and in the opinions of the reporters usually with success. My interest in the subject arose from observations made on two patients who were injected subcutaneously after unsuccessful attempts at intravenous transfusion. One of the patients, whose cells were never greatly diminished, showed a decided rise in hemoglobin, and the second patient showed a marked rise in both hemoglobin and cells. Unfortunately for the experiment, however, both patients were given iron. I then purposely employed the subcutaneous rather than the intravenous route in three patients who received no drug. The blood was citrated. With the exception of Ann F., who was given blood from her mother, all patients' blood groups were determined and a blood given whose corpuscles would not be agglutinated by the recipient's serum.

Two were University Hospital patients and on them was made the study which is reported in the second portion of this paper. The pertinent clinical data from all five cases is presented in Table 1. The Dare hemoglobinometer was used in the three private cases and the Fleischel-Miescher instrument was used in the University Hospital cases. The hemoglobin and red blood cell estimations were made in the private cases by a trained laboratory technician, and in the University Hospital cases by Dr. Ott, the resident in pediatrics. The results are as reliable as one can expect from the method employed.

It is apparent that the injection was usually followed by an increased hemoglobin percentage.

PART II.

Karst,[1] in 1873, noted that blood injected subcutaneously caused a transitory swelling only—and hastily concluded that it was absorbed

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* Read before the American Pediatric Society, June 2, 1920.

[1] Karst: Injectionen von defibriniertem Blute ins Unterhautbindegewebe, Berl. klin. Wchnschr. **10**:587, 1873.

into the circulation. Later workers, Bareggi,[2] Orth,[3] Müller[4] and others, showed that after such injections, the more remote as well as the neighboring lymph glands became swollen and engorged with blood cells, and that within an hour thereafter large numbers of red blood cells were to be found in the thoracic duct.

As bearing on this point of the absorption into the circulation of extravascularly introduced blood, it is to be noted that Hayem[6] after peritoneal injection of dogs' blood into goats recovered dogs' corpuscles from the circulating blood of the latter.

Recently Scott[6] and Hanson injected stained foreign corpuscles subcutaneously and later found them in the recipient's circulation. We can accept as proven the thesis that subcutaneously injected red blood cells are qualitatively capable of reaching the recipient's circulation.

How many cells do so?

It occurred to me that the method devised by Ashby[7] for determining the length of life of the transfused corpuscle offered a way to the solution of the problem.

The method was applied in the two University Hospital cases, Nos. 16706 and 16895. The bloods of these two patients were in Groups III and II. Before receiving the blood injection, their own blood cells were counted, Group II serum being used as a diluent in the hemocytometer in the first case, and Group III serum in the second. Counts of the unagglutinated cells were made on the day preceding the injection and on the first and fifth days thereafter.

Ashby's technic was followed exactly—and all counts were made in duplicate and accompanied by control counts to check the continued agglutinative capacity of the serum.

Table 2 presents the results. In the last column is shown the estimated number of unagglutinatted cells per cubic millimeter which would have been present had all the injected blood cells reached the recipient's circulation. It is evident that this number was never approached and that even five days after the injection the number of unagglutinatted cells was not definitely increased.

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[2] Bareggi: Arch. per le scienze med. **7**, No. 4, quoted by Wm. Hunter, op. cit.

[3] Orth: Beitrag Zur Kenntniss des Verhaltens der Lympdrüesen bei der Resorption von Blut-extravasaten, Virch. Arch. **56**:269, 1872.

[4] Müeller: Untersuchungen üeber das Verhalten der Lymphdrüesen bei der Resorption von Blut-extravasaten, quoted by Wm. Hunter, op. cit. 1879.

[5] Hayem: De la transfusion peritoneale. Compt. rend. **88**:749, 1884.

[6] Prof. F H. Scott, personal communication.

[7] Ashby: The Determination of the length of life of transfused blood corpuscles in man, J. Exper. Med. **29**:267, 1919.

TABLE 1.—CLINICAL DATA

Case	Diagnosis	Age	Amount Blood Injected, C.c.	Body Weights and Red Blood Cell and Hemoglobin Estimations														
				Before Injection			1 Week After Injection			2 Weeks After Injection			3 Weeks After Injection			4 Weeks After Injection		
				Weight, Gm.	Red Blood Cells	Hemoglobin, per Cent.	Weight, Gm.	Red Blood Cells	Hemoglobin, per Cent.	Weight, Gm.	Red Blood Cells	Hemoglobin, per Cent.	Weight, Gm.	Red Blood Cells	Hemoglobin, per Cent.	Weight, Gm.	Red Blood Cells	Hemoglobin, per Cent.
Marj. G. Received iron	Rickets, anemia	10 mos.	75	6,750	4,712,000	27	....	....	....	6,750	....	47	....	....	....	6,825	....	66
Paul H. Received iron	Celiac disease	2½ yrs.	100	7,960	2,776,000	43	9,000	3,900,000	50	....	....	....	9,000	3,984,000	6 8			
Ann F.	Anemia	8 mos.	60	6,250	4,630,000	25	....	....	....	....	....	....	....	....	....	6,775	4,200,000	35
Univ. Hosp. No. 16706	Purpura hemorrhagica	7 yrs.	130	26,000	4,750,000	75	....	....	69	....	4,270,000	73						
Univ. Hosp. No. 16895	Hemophilia	2 yrs.	100	13,400	5,200,000	47	....	....	60	....	4,420,000	70						

Recently, after consultation with me, Giffin and Ashby, at the Mayo Clinic, carried out a similar experiment on an adult who had pernicious anemia. Dr. Ashby has sent me the results with permission to publish them. The patient received 250 c.c. of blood subcutaneously. His average initial nonagglutination count was 50,000 and the post-injection count was 97,350. Ashby estimates that the increased number of cells should in this case equal 250,000 and states that if any of the blood got into the circulation it was only a fraction.

This is entirely different from Ashby's results on intravenously transfused individuals as reported in her work on the length of life of the transfused corpuscle. For example, the initial nonagglutination count in one patient, an infant weighing 20.5 pounds, was 54,400. He was given 220 c.c. of blood, and his unagglutinated cells rose to 1,175,000.

TABLE 2.—Counts of Unagglutinated Red Blood Cells Before and After Injections of Group IV Blood, the Counting Media Being Agglutinative to the Recipient's Own Cells But Not to Those Given Him

Case Number	Weight, Kg.	Recipient's Own Blood Group	Serum Used as Counting Medium	Amount Blood Injected, C.c.	Numbers of Unagglutinated Corpuscles per C.c.			
					Day Preceding Injection	Day After Injection	Five Days After Injection	Theoretical Number if All Injected Blood Had Been Absorbed
16706	27.0	III	II	130	48,400	50,550	100,350	350,000
16895	13.4	II	III	100	189,750	132,825	162,450	780,000

Subcutaneous injection of blood is usually followed by a rise in hemoglobin percentage: but only a small fraction of the cells so injected reach the circulation of the recipient.[8]

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8. The following references may also be consulted:

Hirsch: Ueber subcutane Blut-transfusion nach der von Ziemessenschen Methode, Berl. klin. Wchnschr. **25**:790, 1888.

von Ziemssen: Ueber subcutane Blut-injection und ueber eine neue Methode der intravenösen Transfusion, Verhandl. Inner. Med. Elfter Congress 166-175, 1892.

von Ziemessen: Subcutaneous Blood Injections, J. A. M. A. **9**:35 (July 9), 68 (July 16) 1887.

Sicard: Homohémothérapie sous-cutanée, LaPresse méd., **33**:304, 1918.

Hunter, Wm.: Intraperitoneal Blood transfusion and the Fate of absorbed blood, J. Anat. & Physiol. **21**:138, 264, 450, 1886.

PNEUMOCOCCUS PERITONITIS IN INFANCY AND EARLY CHILDHOOD

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Pneumococcus peritonitis is a rather rare disease among infants and young children. The great majority of the patients in the Babies' Hospital are under 2 years of age, although those up to 4 years are admitted. In the last thirteen years there have been treated 171 cases of general peritonitis of which nine have been proved bacteriologically to be of pneumococcus origin.

This form of peritonitis has been well described by Jensen,[1] Brunn,[2] Annard and Bowen,[3] Rischbieth,[4] Cameron [5] and Abt.[6] It is not the purpose of this paper to duplicate their work, but to point out some of the peculiar features which this disease presents during very early life.

The pathology of the peritoneal inflammation is a purulent fibrinoplastic exudate which involves the whole peritoneal cavity. If the patient lives, adhesions form in the exudate which limit the process, finally causing a localized abscess. In this it differs from other forms of purulent peritonitis seen in children. The source of infection of the peritoneum is undoubtedly through the blood stream. Where the blood has become infected has been a matter of controversy. Barling concludes that the lungs are the primary focus in most cases. Brunn considers the middle ear as the chief portal of entry for the pneumococcus. Annard and Bowen, Jensen and Cameron think the intestines are most often the source of the infection. From a study of our cases it appears that in young children the source is most frequently the lungs. In seven of our nine cases distinct pulmonary symptoms preceded the peritoneal inflammation. Two were apparently idiopathic. No source of the infection of the peritoneum in these two latter cases could be found either in the lungs or elsewhere in the body. It is probable that the pneumococcus usually enters through the respiratory tract, and that it may enter the blood stream without localizing in the lungs. This probably explains the peritonitises apparently idiopathic in origin. There is no evidence in the cases reported

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1. Jensen, J.: Lanngenbeck's Arch. f. klin. Chir. **69**: 1903.
2. Brunn, M. von: Beitr. z. klin. Chir. **39**:57, 1903.
3. Annard, W. F., and Bowen, W. H.: Lancet **1**:1951, 1906
4. Rischbieth, H.: Quart. J. Med. **4**: 1911.
5. Cameron, H. C.: Brit. J. Child. Dis. **9**:288, 1902.
6. Abt, I. A.: New York M. J. **105**:769 (April 28) 1917.

here that the middle ear or the intestines are the sources of infection with the pneumococcus.

The following nine cases show that clinically two types of the disease are met with: (1) Those which are clearly secondary to a pneumonia or an empyema and (2) those which are apparently primary. The onset of the first may be unattended by any definited symptoms or these symptoms may be so slight as to be easily overlooked, and nothing is apparent until the peritonitis becomes localized and abdominal distention is present. The onset of the second group is characterized by symptoms so acute as to immediately overwhelm the patient.

REPORT OF CASES

PNEUMOCOCCUS PERITONITIS SECONDARY TO A PULMONARY INVOLVEMENT BUT WITH NO DEFINITE CLINICAL EVIDENCE OF PERITONEAL INFLAMMATION

CASE 1.—*General pneumococcus infection of all the serous membranes, the meninges, the pleura, the pericardium and the peritoneum.*

A female child, age 16 months, entered the hospital June 19, 1919, with signs of empyema. Drainge of the chest was instituted at entrance and culture of the pus from the empyema showed pneumococci. After the operation the child continued to have a fever. The day before her death, twenty-three days after admission, signs of a meningitis developed and a lumbar puncture revealed a turbid spinal fluid in which pneumococci were found. There were no signs noted referable to the abdomen. The necropsy showed the child to have besides the pneumococcus meningitis and the empyema, a purulent pericarditis and a fibrinopurulent peritonitis. Smear and culture from each of the cavities showed pneumococci.

CASES 2 and 3.—*Pneumococcus infection of the pleura, the pericardium and the peritoneum, but not of the meninges.*

A boy, 2 years old, entered the hospital Oct. 29, 1907, with signs of an empyema. Pus from the chest showed pneumococci. He was in the hospital fifty-four days. There was no vomiting, no abdominal tenderness or distention. The necropsy showed a general purulent peritonitis. The cavity not only contained pus, but the intestines were matted together in many places by an exudate of fibrin. In this case there was also a purulent pneumococcus pericarditis complicating the empyema.

A boy, aged 13 months, came into the hospital April 10, 1920. Physical examination revealed a fibrinous pleurisy. The heart sounds were distant, but pulse was regular and full. The abdomen was negative and there was no vomiting. The child died the sixth day after admission. Necropsy showed a bronchopneumonia with a greatly thickened pleura, an adhesive pericarditis and a general purulent peritonitis. Culture of each showed pneumococci.

It is noteworthy that in each of these three children all or nearly all of the serous membranes of the body were infected. This widespread pneumococcus infection is a peculiarity of early childhood and occurs not infrequently. The three cases illustrate that a pneumococcus peritonitis may exist and that it may have progressed to the point where adhesions were formed and not produce any symptoms sufficient to attract attention.

In the next group of cases, four in number, the peritonitis was the only complication of the pulmonary involvement; these children lived until abdominal distention was present, or until a complete recovery had taken place. They illustrate the onset of symptoms, although it is evident the disease must have begun previously.

PERITONITIS, SECONDARY TO A PULMONARY INVOLVEMENT AND WITH DEFINITE PERITONEAL SYMPTOMS

CASE 4.—*Peritonitis in which symptoms began with abdominal distention and vomiting three weeks after the onset of pneumonia.*

A male infant, 9 months old, admitted April 2, 1918, three weeks previously had an abrupt onset of cough and fever. These symptoms had continued to admission but were not as severe as at the onset, when the temperature was 104 F. When examined at entrance the abdomen was tense and tender. The child was irritable, drowsy, and apparently acutely toxic. The lungs were negative on physical examination. The leukocyte count was 31,000; 79 per cent. polymorphonuclears. Von Pirquet test was negative. The temperature at entrance was 102 F, which was the average temperature in the three days in the ward. The child vomited almost everything taken and the parents stated that this had been the case for two days previous to admission. The abdomen became more enlarged, but otherwise the symptoms remained practically the same. He died in three days. Necropsy showed a small localized empyema at the base of the right lung and a diffuse purulent peritonitis. The culture from the chest and peritoneum was pneumococcus.

CASE 5.—*Peritonitis in which symptoms began with abdominal distention five weeks after the onset of pneumonia, and three weeks after an operation for empyema.*

Sept. 7, 1911, a boy, aged 2 years, was admitted. Eight weeks before admission he had had an attack of pneumonia. In two weeks this was complicated by an empyema for which he was operated on. Although the operation wound had healed, an afternoon fever had persisted. Three weeks before admission gradual abdominal swelling had begun. Physical examination at entrance showed a distended abdomen. A definite circumscribed mass was easily palpable in the left lower quadrant, which it almost completely filled. Examination of the chest revealed an unresolved pneumonia at the site of the empyema cicatrix. The temperature was normal; the leukocyte count was 14,500; 72 per cent. polymorphonuclears. The child died ten days after admission. A postmortem examination was not allowed, but the abdominal mass was aspirated and 30 c.c. of pus was withdrawn, the culture of which showed pneumococcus. Aspiration of the thorax was negative.

CASE 6.—*Peritonitis in which abdominal symptoms began one week after the onset of pneumonia.*

A boy, 4 years old, entered March 10, 1917, with a history of an acute fever one month before. No diagnosis was made. The fever had subsided in a week, but after this the parents noticed the abdomen began to enlarge. At entrance the abdomen was distended and tender, and there was distinct fluctuation at the umbilicus, below which there was an area of dulness impossible to map out distinctly because of pain to the child. Over the base of the left lung there was dulness and suppressed breathing. The temperature was normal; the leukocyte count was 27,000, 64 per cent polymorphonuclears. Tuberculin skin test was negative. The day after entrance an incision was made through the umbilicus, and nearly a quart of pus was removed. The culture from this showed pneumococcus. Eight days after admission the pulmonary signs had disappeared and the boy made an uneventful recovery.

CASE 7.—*Peritonitis in which symptoms began about a week after the onset of pneumonia.*

A girl, 2½ years old, entered the hospital Jan. 30, 1918, because of enlargement of the abdomen. Six weeks before admission she had had pneumonia. This trouble subsided in five days, and a few days later the abdominal swelling was noticed. This was present to a marked degree at entrance, and there was fluctuation at the umbilicus. A mass which extended across the abdomen midway between the xiphoid and umbilicus was interpreted as being a tuberculous omentum. The physical examination was otherwise negative. The temperature was normal and again the von Pirquet test was negative. The leukocyte count was 15,000; polymorphonuclears 76 per cent. An incision was made at the umbilicus, and 13 ounces of pus was evacuated, which was found to contain pneumococcus. The child nearly recovered in two weeks when she was discharged from the hospital on account of the onset of varicella.

These seven cases indicated what is probably the usual course of a secondary pneumococcus peritonitis. In none of these children was the onset of the peritonitis marked by definite abdominal symptoms. Previous to the time when distention was first noticed there was no tenderness, rigidity, pain, nor was there any vomiting. The infection of the peritoneum may rapidly follow the pulmonary infection, as in Cases 6 and 7, or it may not be present for weeks, as in Case 2. Pneumococcus peritonitis begins in a general inflammation which very quickly becomes localized by the formation of adhesions. While this is taking place, there is usually moderate fever, the abdomen gradually enlarges and occasional attacks of vomiting may occur. Palpation of the abdomen discloses one or more masses which may be met with in any part of the abdomen.

In a diagnosis of this condition, tuberculous peritonitis would certainly have to be excluded. Of first importance is the tuberculin skin reaction. A preceding attack of pneumonia or empyema would suggest that the peritonitis was caused by the pneumococcus. The rapid progress of this disease is not characteristic of tuberculous peritonitis.

A study of these cases shows that in pneumococcus peritonitis the patients rarely die from that disease, but from associated conditions.

The treatment of pneumococcus peritonitis illustrated in these seven cases should be expectant until the inflammatory process has become circumscribed and an abscess is formed. At that time incision and drainage of the abscess is indicated.

IDIOPATHIC PNEUMOCOCCUS PERITONITIS

The so-called idiopathic or primary pneumococcus peritonitis is just as characteristic in its course as the type just discussed. The two cases reported here terminated fatally. Rischbieth and others report recoveries but they were in older children. It is rare for one of these patients to recover.

Cases 8 and 9.—*In the following cases neither the history nor the physical examination nor the necropsy showed any disease besides the peritonitis.*

A girl, 2 years and 10 months old, entered the hospital April 24, 1911. Six days before she had had an acute vomiting attack, and became prostrated immediately. She complained of pain in her abdomen which was held rigid. Fever had been varying between 102.5 and 105 F. On the day of entrance, her abdomen was noticeably distended. The physical examination was negative, except for the tender, rigid and distended abdomen. Temperature on admission was 106.4 F. The leukocyte count was 38,000; polymorphonuclears, 88 per cent. The child died six hours after admission. The postmortem examination was negative, except for a general purulent peritonitis. Culture from the peritoneal pus showed pneumococcus.

A girl, 2½ years old, was admitted July 19, 1919. Two days previously she suddenly began to vomit and to complain of pain in her abdomen. The fever was high and there was a diarrhea. From the onset she was acutely toxic. On admission the abdomen was tender everywhere and was held very rigid. The remainder of the examination was negative. Temperature was 102.6 F. In this case there was a leukopenia, the leukocytes numbering only 3,600; polymorphonuclears, 56 per cent. A laparotomy was performed two hours after admission and a purulent peritonitis was found. Culture from the peritoneal exudate showed pneumococcus. The temperature remained elevated, although there was always free drainage from the incision. Other symptoms remained unchanged. She died four days after admission, six days after the onset. The necropsy revealed nothing besides the general purulent peritonitis which, however, showed signs of becoming localized by the formation of adhesions.

These two cases, which in many respects closely resemble each other, enable one to form a distinct clinical picture of this type of pneumococcus peritonitis. The abrupt and stormy onset differs from the very similar peritonitis of streptococcus origin when that is apparently idiopathic. Rabinowitz[7] has reported a number of these cases and he calls attention to this differential point. Clinically, the two conditions are indistinguishable, except that in idiopathic streptococcus peritonitis the onset is more often gradual. Acute appendicitis may simulate primary pneumococcus peritonitis but in this disease the symptoms are not as acute. In appendicitis the temperature usually is lower, and well marked localized tenderness is present.

The treatment of these cases is a debated point. It is the general opinion of writers on this subject that the abdomen should be opened. In Case 8, the child was not operated on and in Case 9 the child was operated on. It is significant that the course of the disease was so similar in these two children and it seems evident that nothing was gained by opening the abdomen. The pathology of the disease suggests the form of treatment. These, as well as cases of the first two groups, early tend to form a localized abscess and apparently opera-

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7. Rabinowitz, M. A.: Am. J. M. Sc. **157**:797 (June) 1919.

tion is of no benefit until that localization has taken place. The best treatment would seem to be to keep the patient fully under the influence of morphia and by this method keep the intestines at rest and provide stimulation for the child. If the vomiting is severe, hypodermoclysis is indicated.

I wish to thank Dr. L. Emmett Holt for the privilege of reporting these cases, and for his assistance in the preparation of this paper.

Thirty cents each will be paid for the following issues of the American Journal of Diseases of Children: January, 1913; February, March, November and December, 1914; January and August, 1915; January, 1918; March and April, 1919. Address to AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Ill.

American Journal of Diseases of Children

Vol. 20 NOVEMBER, 1920 No. 5

A POLYNEURITIC SYNDROME RESEMBLING PELLAGRA-ACRODYNIA (?) SEEN IN VERY YOUNG CHILDREN *

REPORT OF CASES

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During the past five years [1] there have appeared in this clinic seventeen patients, all under 4 years of age (five of them being less than one year old) who have manifested a group of signs and symptoms out of the ordinary. The resemblance of their malady to pellagra was striking, but so many points spoke against such a diagnosis, that it was necessary to think of the presence of some other disease. Extremes in severity of this affection were encountered, depending usually on the duration of the illness, some cases being very mild, others ending in death shortly after admission to the hospital. It is possible, however, that had we then realized the importance of forced feeding as a therapeutic measure, two of the patients who died, might have been saved.

CLINICAL PICTURE

The disease picture was a complex one, the nervous system and the skin being most involved, while the respiratory tract and the digestive tract appeared to be less affected. On the part of the nervous system the changes were chiefly sensory or trophic in character. Alopecia, pulling out of the hair (trichotillomania), falling out of the teeth with only slight involvement of the gums; photophobia, and in one case double neurokeratitis; changes in the nails, and reddening of the tongue were seen. Paresthesia of the toes and feet, and of the fingers and hands was another constant and often most distressing symptom, leading the children to rub, scratch and even chew the extremities. A diminution in cutaneous sensibility to pin pricks was made out in some of the cases but this seemed not to be a constant finding, due

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[1] This affection was first reported in a paper entitled: A Series of Trophoneuroses Probably Due to Infection, read by title before the Section on Diseases of Children, J. A. M. A. **68**: 1851, No. 24, 1917.

possibly to the difficulty of making accurate observations in individuals so young. The reflexes were diminished in almost all cases, absent or increased in some; but the severity of the disease and the degree of loss of reflexes did not necessarily coincide. In the more severe and even in the mild ones dulness and apathy, alternating with extreme restlessness and sleeplessness, and in one instance, delirium, were observed. In a clear cut case the patient would often adopt a characteristic posture, either lying on the side, rubbing the hands or feet, or crouching with the head burrowed into the pillow. In few diseases seen by me has a clinical picture of such intense wretchedness been presented.

Skin.—The skin manifestations were most uniform, and were quite definite as far as the fingers and toes were concerned—less so on the trunk. A symmetrical involvement of the fingers and toes, recurring at intervals of a fortnight or so, or even tending to be more or less constant, was one of the most striking characteristics of the trouble. With the hands and feet cyanotic and cold, especially when the temperature of the surrounding atmosphere was low, there appeared a nonconfluent erythematous rash, most marked at the tips of the fingers and gradually diminishing until at the region of the wrist it had quite faded away. In some of the cases a small number of fine papules rose from these areas of erythema. Confluent erythema was the rule on the distal phalanges. Desquamation, most marked at the tips of the fingers and toes, growing less toward the region of the wrists and ankles was often present. The feet were only slightly less involved than the hands. Never was there observed anything like the clear-cut line of demarcation between affected and untouched skin as in pellagra. When the thorax or the proximal portions of the arms and legs showed skin manifestations, these consisted either in a morbilliform breaking out or in bullae—the latter being seen only in very severe or advanced cases.

Pustules were uncommon although in one instance death took place from deep phlegmon. When an eruption appeared on the body it was usually accompanied with paresthesia, and in one instance at least, it was so severe that the possibility of a prurigo ferox was considered. With the passing away of the body eruption, pigmented spots were sometimes left. In two of the cases the cheeks and the tip of the nose were involved. The buttocks occasionally showed some skin changes but the region of the crotch was usually spared. The back of the neck was never seen to have any localized breaking out or scaling as in pellagra. The skin eruption was at times of short duration. In three of the cases the disease ran a course without more than the initial erythema which had all but disappeared by the time the child came to the hospital, although the systemic manifestations were still present in marked degree. Some desquamation about the finger tips was the only evidence of a previous skin affection.

Hair.—The pulling out and falling out of the hair was present in a number of cases which were of more than a month's duration. As a result of this such patients would present themselves with a very scanty covering of dry hair or actual baldness, limited usually to the crown of the head. Some peculiar sensory disturbance must have caused the children thus affected to actually take the hair out "by handfuls." Scratching of the scalp was never observed, so that this symptom could not be attributed to abnormal sensation of the skin.

Teeth.—The loosening and falling out of the teeth was likewise a surprising manifestation, especially since there was no previous evidence of pathology manifested by the gums. One mother stated that she thought that a tooth was growing abnormally long and was protruding from the mouth like a fang. On taking hold of it she was astonished to find it loose and separated from the socket. In other cases the gums at times were slightly swollen and a deposit noted around the teeth; but these changes would not have led any one to hold them responsible for the tooth loss. There was no adherent tissue, blood or exudate on the lost teeth.

Nails.—The nails were rarely involved—one only showing trophic darkening and softening. Some of the toe nails in this case were lost but the finger nails remained in place.

Gastro-intestinal Tract.—An extreme and obstinate *anorexia* was a prominent part of the disease picture. Indeed, it was the failure to recognize the gravity of this symptom in some of the earlier cases which probably led to a fatal outcome. In only one instance was *diarrhea* present either before or after admission to the hospital. On the other hand, in about one quarter of the cases we were impressed with the fact that the transverse and descending colon were filled with hard fecal masses. *Vomiting* was never found or complained of before admission. Failure to take a sufficient quantity of food would seem in large part to be responsible for the marked degree of *emaciation* which was almost invariably present in those children who had been sick for several months before being brought to the hospital. Many of the patients suffered extreme *thirst.* Unusual *sweating* was common in the well advanced cases.

Genito-urinary Tract.—Frequency of urination was, however, an almost uniform symptom and this was probably accompanied with distress, as many of the children kept crying their desire to empty the bladder. Involvement of the genito-urinary tract was manifested by the frequent presence of *pyelitis,* though this was never extreme and usually yielded to treatment.

The severity of the disorder varied. Two of the patients seen in the beginning of the study (summer of 1915, winter of 1916) died because we seemed unable to arrest the advance of the morbid process, but it should be noted that forced feeding was not tried in these cases. It is our impression also that, with one possible exception, the cases which we have seen in the last three years were milder than those seen earlier. One patient, however, was brought here several months ago with an advanced pulmonary tuberculosis as a complication, and in this instance death took place three days after admission to the hospital. Several of the cases, on the other hand, were very mild and yielded to symptomatic and expectant treatment. The duration of the trouble varied from two to eight months.

Laboratory Examination.—Laboratory findings showed a certain uniformity and of these the *leukocyte count* was especially noteworthy. With the exception of one case in which only 9,000 leukocytes were found, the number ranged from 11,000 to 30,000. In the differential count, however, there was no corresponding increase in the polymorphonuclear cells, an average of 65 per cent. being observed. Eosinophils, up to 2 per cent, were sometimes encountered, due possibly to the skin involvement

The *stomach contents* were twice analyzed and in both instances a practically normal amount of hydrochloric acid found. *Acetonuria* was a rather common finding. This was in all probability due to the state of under nutrition produced by the marked anorexia. Pus cells were frequently found in the urine, but this certainly could not be regarded as an essential part of the disease picture. The *spinal fluid* occasionally showed a slight increase of globulin but the cells were not abnormally increased. The *Wasserman* test was uniformly negative.

COMMENT

From these findings it seems probable that we are dealing with a primary disease of the nervous system. The falling out of the teeth (in three cases) without a distinct involvement of the gums, the falling out of the hair and a double neurokeratitis (first case) point quite clearly to an involvement of the fifth nerve. The paresthesia of the extremities and of the trunk also suggests a sensory nerve involvement, while the coldness and blueness of the finger tips and toe tips point to a vasomotor disturbance. The muscular weakness and atrophy, the diminution of the reflexes and, at times, their complete absence suggests involvement of the lower motor neuron, even though a complete palsy was not commonly encountered. In other words, there seems to have been a preponderance of sensory manifestations with a mild affection of motor nerves.

ETIOLOGY

Diet.—With the recent increasing interest in systemic nutritional disorders, such as pellagra, beriberi, and scurvy it was natural that this very definite group of symptoms should suggest the possibility that we were dealing with a deficiency disease; but from the beginning, the histories taken failed to show that the diet was at fault. This was especially emphasized in the case of the four[2] babies under 1 year of age, who had been breast fed for a considerable time. In two of these certainly, the disease began while the baby was still taking the nurse—one from a mother who not only ate "everything" but also a "very great deal of it." In analyzing this mother's diet, we were unable to determine a distinct lack of any of the major organic constituents, the salts, including calcium, or the known vitamins. The questioning in this instance was carried on by three observers. The diet of the other three nursing mothers might possibly be questioned.

Many of the older children in this series had not been receiving a diet complete in every respect; but the omissions were not sufficiently definite to give unmistakable proof of a causal connection. In some cases we found that the children did not take milk but did take vegetables and eggs, while others took enough milk but refused to partake of green vegetables and fruit. Their diets, on the whole, were certainly no worse than those of the average child coming to our clinic.

Food.—The effect of food on the course of the disease was studied in those patients who entered the hospital, more especially in the more recent cases. A corrective diet, complete in every respect, so far as we know, supplying an adequate number of calories, sometimes introduced by gavage, was given. The benefit from this treatment was unmistakable, although cure was not always brought about quickly; for the paresthesia and weakness were most persistent. The improvement by feeding, most prompt in mild and less well advanced cases, was the only evidence of a possible relationship between food and the disease. We have not yet tried to determine which constituent of the food is most helpful. In one of the early cases (the patient died later) there was added to the diet the antineuritic vitamin (water-soluble B.).[3] No influence on the course of the disease was discernible.

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[2] Cases 7, 8, 12 and 17.

[3] The material was prepared by adsorption from autolyzed yeast by Dr. A. Seidell and through his kindness sent here for use in these cases.

Respiratory Infection.—From the beginning of our observations we were impressed by the fact that respiratory infection [4] must play a prominent part either as a primary or secondary cause of the trouble, and as the number of cases seen increased, this feeling was only strengthened. It was so common to have the parents, without suggestion or pressure, volunteer the information that the trouble commenced with a bad cold or followed shortly afteward; or after influenza, that we were forced to regard the respiratory infection as more than a mere coincidence. This feeling was further strengthened by the experience in the fourth case in which radical surgical treatment of the nose seemed quite definitely to arrest the unfavorable course of the disease, while the two previous patients, whose illness appeared to be of about the same degree of severity, died.

Focal Infection.—In two of the sixteen cases a rather interesting, even if not conclusive, comparative experience may be related. In one of these, a baby of 10 months, tonsillectomy performed after one month's observation in the hospital seemed to have caused a complete disappearance of the signs and symptoms in six weeks' time. In the other case, seen at the same period (1918), the operation was refused. In this latter case paresthesia and some weakness were still present after seven months. Another finding which indicates that infection plays some part in the disease was the leukocytosis referred to above. We were inclined, in fact, to base our prognosis in the operative cases on the leukocyte count. Thus if the count remained high, we did not expect rapid improvement. In a small number of cases most careful questioning of the parent failed to reveal anything resembling an acute respiratory infection at the onset and it must be admitted that one cannot easily explain these exceptions, unless one assumes that such infection was latent or overlooked.

Diphtheria.—The questioning of a possible relationship between a diphtheria or diphtheria-like organism, which we found in the nasal cultures in most of these cases, was considered in view of the regularity of their appearance. Some of these organisms have been found to be highly virulent for guinea-pigs; diphtheria antitoxin does not give protection. The description of a case seen elsewhere,[5] in which nasal diphtheria was definitely known to precede a case of this kind, together with the fact that in Jacobi's Treatise on Diphtheria [6] mention was made in a few lines of this same affection appearing as an occasional sequel of diphtheria, seems to be somewhat suggestive. A positive Schick test, however, was never obtained and, furthermore, diphtheria antitoxin was without the least therapeutic benefit. In one case a test for circulating diphtheria toxin seems to have been positive, but here, again, antitoxin was absolutely without therapeutic effect. We have not thus far been able to bring forth any evidence that the diphtheria-like bacilli found played an exciting rôle.

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[4] See reference 1.

[5] Personal communication of Dr. Thomas B. Cooley, Detroit.

[6] Jacobi, Abraham: A Treatise on Diphtheria, 1880, p. 146.

A postmortem examination was made in one case, that of a child suffering with an advanced pulmonary tuberculosis. In this case, besides the extensive changes in the lungs which had no direct bearing, there were in addition some interesting changes made in the central nervous system. In the spinal cord gliosis about the central canal was present. Of the anterior horn cells occasionally one or more of these situated proximal to the anterior commissure was found to be of poor staining quality. The dorsal columns did not show the effects of the disease.

The sciatic nerve showed edema and swelling of the myelin sheath, as well as edema of the connective tissue about the nerve fibers. No cellular infiltration was observed. The same variation in the size of the fibers was seen in the posterior roots in the lumbar cord. Edema and swelling of the myelin sheath were also seen in the fibers of the dorsal root in that portion of the nerve lying between the ganglion and the spinal cord.

Heredity.—In no case was there any evidence of involvement of the parents with this disease or anything resembling it. In Case 7, so strikingly benefited by tonsillectomy, a brother, 1½ years of age, died of what was undoubtedly this same effection. Most of the patients lived in rural districts, only two of them coming from a town as large as 40,000. Furthermore, intense poverty was not necessarily present in the families in which the disease occurred. One can draw no definite conclusions as to the time of onset as far as season is concerned, although none of our cases had their onset in July, August or September. Of the seventeen cases, seven began in December, January and February. Two, however, were supposed to have shown initial symptoms in June. The accompanying table suggests that the disease is increasing in frequency.

NUMBER OF CASES OBSERVED DURING A PERIOD OF FIVE AND ONE-HALF YEARS

Year	No. of Cases
1915	2
1916	3
1917	0
1918	2
1919	4
1920 (to June)	7

DISCUSSION

Deficiency Disease.—The symmetry of the skin eruption, together with some of the other signs and symptoms of the disease, called to mind the possibility that we were confronted with one of the deficiency diseases, more probably pellagra, and when we bore in mind the "protean" character of this latter disease we were, for a while at least, inclined to favor this diagnosis even though there were a number of points open to question. Without going into a detailed discussion, a number of marked differences seem to differentiate the clinical picture of this disease from that of pellagra. These are:

1. Lack of a sharp line of demarcation in the skin lesion.
2. Lack of definite or common dietary error.
3. Uniform age of the patient.
4. Absence of history of pellagra or pellagra-like disease in the family.
5. Absence of digestive symptoms except constipation and anorexia.
6. Lack of recurrence in cured cases.
7. Low incidence of pellagra or a similar disease in adults in this region.
8. Occurrences in several instances in breast-fed babies.
9. Frequent history of infection.
10. Duration of subjective symptoms (seven months in one case).
11. Aggravation of symptoms in cold weather in contrast to pellagra.

Motor Neuritis.—The diminution of the reflexes might suggest a motor neuritis similar to beriberi, but the preponderance of sensory symptoms is so definite as to speak strongly against such a diagnosis even though sensory symptoms are included in the description of beriberi.[7] In this connection we have, however, the interesting experience of Moszkowski[8] who partook of polished rice as his sole ration. He developed symptoms chiefly sensory in character. We are not at this time, however, justified in completely ruling out the question of the existence of a deficiency disease similar to beriberi as a part of the clinical syndrome.

Arsenic Poisoning.—The possibility of arsenic poisoning was excluded in two instances at least, by the analysis of the urine. Clinically, the slight motor signs and symptoms would scarcely lead us to expect such a cause. Ergotism and other similar intoxications are apparently very different from the disease under discussion.

Trophoneurosis.—Another group of diseases suggested by these cases are the so-called trophoneuroses, such as acroparesthesia and erythromelalgia. While there is a slight fundamental similarity, there is no case of which the description will fit in exactly with what we have seen in our patients. Trophoneuroses are usually seen in adults and one of them, acroparesthesia, chiefly in women.[9] A case reported by Adams[10] as erythromelalgia seems to have been more like one of our own cases.

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[7] Manson, Sir Patrick: Beriberi, Allbutt & Rolleston, System of Medicine, London, 1910, **2**: Part 2, p. 630.

[8] Moszkowski, M.: Reviewed in Deutsch. med. Wchnschr. **39**:1479, 1913.

[9] Cassirer, R.: Die Vasomotorisch-trophischen Neurosen, Lewandowski, Handb. der Neurol. **5**: p. 220.

[10] Adams, S. S.: A Case of Erythromelalgia, Tr. Am. Ped. Soc. **25**:63, 1913.

Other Diseases.—A number of points of resemblance with other diseases is not without interest. The falling out of the teeth has been occasionally noted in *tabes dorsalis.* The marked subjective symptoms resemble those of *dermatitis herpetiformis,* even though the skin manifestations of this latter disease are quite different. The lowering of resistance to infection noted in the later stages of the disease as evidenced by our two fatal cases is found in *paralysis of the insane.* Spurgin [11] described what he calls "acute pellagra or dermatitis exfoliativa" occurring in a boy of 20. This patient had a high temperature and paresthesia together with an erythematous and papular eruption on the exposed surfaces followed by desquamation.

Other evidences of a possible causal relationship between infection and the syndrome under discussion may be derived from clinical experience. The frequency with which the hair falls out in scarlet fever and other acute infectious diseases is familiar even to the laity. The presence of sensory manifestations in motor neuritis (polyneuritis) is touched on, even if not emphasized, in most works on neurology, but for some reason the chief medical interest has always seemed to have been in the paralytic phenomena, whereas paresthesias, skin eruptions and the like have attracted less attention. Diphtheria with its tendency to be followed my motor neuritis has not yielded many sensory syndromes such as those which we are describing.[12]

The case referred to by Jacobi [13] is of special interest in this connection, and the following quotation makes it quite probable that he was dealing with a case of this peculiar affection. "Besides the above mentioned, there may be general debility of the muscular system, atrophy of the skin and nutritive disorder with alopecia and disorder of sensibility, not always of the subjective type." Pflugbeil [14] reports seven cases of erythematous vesiculopustular eruptions with marked sensory symptoms in adults. These cases differed also from our own in that they were closely associated in point of time with an acute infection and appeared even at the height of the illness.

Acrodynia.—What, then, is this interesting disease? Weston [15] after a careful review of the literature states that we are dealing with acrodynia or "epidemic erythema" described about 1828.[16] From descriptions of the disease there appears to be a marked similarity between our cases and acrodynia. Babes and Sion[17] state that in acrodynia conjunctivitis with considerable swelling is always present. Spasticity and convulsions are also included as symptoms. We have never noted any such condition.[18]

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[11] Spurgin, W. H.: New York M. J. **98**:1070, 1913.

[12] Barabas, Z.: Sensible Störungen bei postdiphtheritischen Lahmungen, Jahrb. f. Kinderh. **82**:476 (Dec.) 1915.

[13] See reference 6.

[14] Pflugbeil, E.: Beitrag zur Akuten Postinfektiösen Herpetiformen Exanthema. Dermatol. Ztschr. **17**:307, 1910.

[15] Weston, William: Acrodynia, J. A. M. A., April 30, 1920.

[16] Dictionnaire de Medecine, Pàris, 1832, p. 524-5, 1; Numerous epidemics of affections in which disorders of sensibility were prominent had been reported previous to this.

Influenza.—The heaping up in "epidemic" form (eight cases in Portland, Ore.,[19] thirteen cases in Cincinnati, Ohio[20] and sporadic cases throughout the middle west[21]) at this time, brings up an interesting possibility, namely, that we are dealing with a sequel of influenza. It may be more than a coincidence that the first report of acrodynia appeared in 1828,[22] within a year or so of the first pandemic of influenza of the 19th century. The affinity of the virus of influenza for the nervous system is well recognized. Leichtenstern[23] states that "there can be no doubt but that influenza has been the direct cause of numerous polymorphic diseases of the nervous system. The latest influenza pandemic (1889-90) and its recurrences have taught us something quite new in neurology, namely, an acute infectious disease which, compared with all others, is characterized by its striking neurotoxic effects." In our cases we may be having either milder degrees or nerve intoxication, with phenomena of irritation rather than those of destruction, or a virus with a special affinity for sensory nerves, which will explain the peculiar subjective and sensory qualities of the disease. The cases seen before the height of epidemics may be explained either by the sporadic occurrence of influenza, or by the fact that more than one virus can act as a causal agent.

If it is borne out by further investigation that we have an infectious polyneuritis, it may be well to dispense with the older names. It is desirable to have the name indicate the preponderance of sensory signs and symptoms and bring it into contrast with the ordinary or motor form of polyneuritis. As stated above, there is more evidence pointing to an infectious than a dietary origin of the disease. It is conceivable, however, that there is an association of both factors: an improper diet may have rendered nerve tissues and cells more vulnerable to the influence of bacterial poisons which have a special affinity for such tissues.

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[17] Nothnagel, H.: Handbuch der Specialen Pathologie und Therapie, Vienna **24**:53, 1901.

[18] Dictionnaire de Medecine, Paris, 1832, p. 524-5, 1; I have preferred to avoid any lengthy discussion as to the identity of acrodynia and the affection reported in this paper.

[19] Cases reported by Weston. See reference 15.

[20] Personal communication of Dr. F. H. Lamb, Cincinnati.

[21] Omaha, Chicago, Detroit, Des Moines.

[22] In 1827 influenza broke out in epidemic form in eastern Russia, especially Siberia, whereas the great pandemics lasted from 1830 to 1833. Glancing over the bibliography of the article "Acrodynie" in the Dictionnaire de Medecine, Paris, 1832, p. 524-5, 1; one finds that the dates of publications of numerous of the articles correspond more or less with the appearance of early influenza epidemics.

[23] Leichtenstern: Influenza, Nothnagel's Practice, Philadelphia and London, 1905, p. 639.

DIAGNOSIS

The diagnosis offers little difficulty when one case has been seen provided the disease picture is moderately or well advanced. There is really no other disease, unless it be pellagra, that could deceive an observer and, with the points of difference indicated above, the distinction can easily be made. In two cases the initial rash was said to have been scarlatiniform, and these cases, when seen in our clinic; did suggest that they might be in the stage of desquamation of that disease. The general wretchedness and emaciation, however, together with the paresthesia of the fingers and toes, which were evident on more close scrutiny, made clear the nature of the trouble.

The milder cases without eruption on the fingers and toes might also tend to be confusing, were it not for the fact that the general constitutional disturbance and the local discomfort of the extremities were always striking. In two of the infants, the symptoms were restlessness and sleeplessness, which might have led to an assumption of a minor ailment, such as the cutting of teeth. A glance at the fingers and toes, and further questioning of the parents as to the nature of the baby's distress led to the correct diagnosis. It is very probable that many of these mild cases are being overlooked in the country at large. In the very severe cases, in which the rash was present also on the trunk, intense pruritis suggested the possibility of prurigo, but the history of our disease differs sharply from the affection. Where bullae are present—again in the severe cases—diagnosis may not be clear if other parts of the clinical picture are not sought for. The falling out of the teeth in patients whose disease is well advanced will also help in the diagnosis.

TREATMENT

The marked emaciation which is the result of persistent aversion to food calls for vigorous treatment, and the patient's life may depend on this. Gavage should be resorted to without hesitation where milk and other proper nutriments are refused. This is, at present, the mainstay of therapy, and when vigorously carried out brings relief. The acetonuria demands treatment with carbohydrates and moderate reduction of fats, but as this metabolic disorder is usually due to "starvation," it disappears in a short time after forced feeding. In the event, however, that the progress to recovery is very slow, or if a fatal outcome is feared, an attempt to remove the assumed foci of infection (tonsils or accessory sinuses of the nose, etc.,) is justified. While our experience with operative measures in the treatment of this disease is not very great, we are, nevertheless, favorably impressed with the results obtained in the few cases observed.

CONCLUSIONS

1. In a series of cases presenting marked sensory symptoms with motor manifestations of less degree, an uncommon clinical picture is described, present chiefly in children under three years of age (one child four years old). It bears a definite resemblance to acrodynia or "epidemic erythema" as suggested by Weston.

2. The disease seems to be increasing.

3. According to the anamneses, infection rather than dietary error seems to play the more important role as an exciting factor.

4. A postmortem examination in one case (complicated with tuberculosis) showed involvement of an occasional anterior horn cell of the spinal cord, gliosis about the central canal and edema of the sensory roots.

5. It is suggested that the disease described is a post influenzal radiculitis or sensory polyneuritis.

REPORT OF CASES

Case 1.—H. B., aged 2 years, female. Family history negative. This baby had been breast fed and then placed on a general diet. Had whooping cough with resulting chronic infection of the nose and throat. For the relief of this the tonsils and adenoids were removed.

Present Illness.—In May, 1915, following a recurrence of nasal infection, a branny desquamation of the hands and feet, followed with emaciation, double neurokeratitis, alopecia and falling out of the teeth took place. The anorexia was marked. When seen in the hospital in September, 1915 (four months after), the most marked symptoms were past, although nasal discharge still persisted. The child was still weak, appetite was poor and slight photophobia was present, as well as some discomfort of the hands and feet. Complete recovery took place. One year later the child was perfectly well. There has never been a recurrence of the trouble.

Laboratory Examination.—Leukocyte count, 12,700. Urine contained pus cells.

This is the first case seen, and was characterized by a rather slow progression, due to the fact that the tonsils and adenoids were early removed.

Case 2.—L. E., aged 2 years and 7 months; female. Family history negative. No questioning as to respiratory infection. Diet unbalanced and characterized by overindulgence in cornmeal.

Present Illness.—The present illness began in June, 1915, the onset being gradual with photophobia, general weakness and constipation After this a rash broke out, first on the chest, abdomen and back, later involving the arms, legs and face. The hands and feet seemed to have been "dipped in hot water." They were red and swollen and subsequently desquamated. No blisters were observed. The itching was marked. The third appearance of the rash occurred just before admission to the hospital, October, 1915. The weakness and emaciation were so great that walking was impossible. Alopecia was still marked at this time. A tooth fell out while the child was eating, the mother hearing it drop upon the floor.

Physical Examination.—On examination, a striking picture was observed. A weak, irritable child, fearing the light and so weak that it could not hold up its head, was seen. There was a mucous discharge from the nose, mucopus was seen in the throat and tracheal râles were made out. After exertion the breathing was labored. A morbilliform eruption was seen on the thorax, abdomen, and outer side of the thighs. Scratch marks and some desquamation were present. The most marked lesions seen were over the swollen fingers where an erythema was present. Toward the wrist and arm the rash was less and became finely papular. A dusky, swollen erythema appeared on the feet in the region of the toes, associated with marked desquamation. A dusky pigmentation at the bed of the nails was seen. An irregular tremor of the hands and knees was present. The child was constantly picking at the hands and feet. Thirst was intense. During the course of the patient's stay in the hospital, two teeth fell out, and on examination of the gums one could see a cleft, but there was practically no inflammatory reaction about the cavity. The lower teeth were firm. The giving of a quantity of absorbed vitamin prepared by Seidell caused not the slightest improvement. Toward the end of the disease the temperature rose, the child became irrational, and phlegmon of the right thigh developed. Death took place shortly afterward.

Laboratory Examination.—Leukocyte count, 17,700. Gastric analysis showed free hydrochloric acid in normal quantity. Urobilinogen was negative.

CASE 3.—E. M., aged 3½ years; male, came from a farm and was first seen in March, 1916, having been sick for three months. The dietary history in this case indicated a small intake of milk and that cornmeal mush was taken three times a week. Eggs were eaten every other day, but green vegetables did not form part of the menu.

Present Illness.—According to the parents' story, the illness commenced with "grippe" and abdominal pain was complained of at the time. The appetite became very poor. Within a month a rash appeared on the trunk and on the hands and feet. The hair fell out early in the course of the disease. A very intense weakness was present. A recurring dusky rash, most marked at the tips of the fingers, followed, with desquamation. General irritability and sleeplessness were marked.

Physical Examination.—On examination, striking alternating periods of irritability and drowsiness were observed. Alopecia of the anterior portion of the crown of the head and coldness of the extremities were noted. Pulse was made out on the dorsum of the foot. The drowsiness, apathy and peculiar mental symptoms increased and death ensued. In this, as in one other case, blebs appeared on the skin a few days before death, which took place by terminal pneumonia. General dietary treatment had no influence on the condition.

Laboratory Examination.—A leukocytosis of 26,100 with 66 per cent. polymorphonuclears was found. A normal amount of combined hydrochloric acid was present on gastric analysis. The blood culture was negative.

CASE 4.—Patient, aged 2 years. This case was very mild in character, and the patient refused to come into the hospital for observation. The records are incomplete as to previous diet and etiology. This patient recovered without special treatment other than a revision of the diet carried out at home. This case was seen in 1916.

CASE 5.—L. O'R., aged 1½ years, male.

Present Illness.—Had the onset of his trouble in November, 1915, and was admitted to the hospital six months later, in May, 1916. He had been breast fed for fourteen months and after this was given food from the table. Diet showed a shortage of milk and greens. He had always been subject to colds. From the onset of the illness this patient had been treated with nasal douches for "catarrh." Again, the same indifferent, half irritable, languid appearance noted above presented itself. The child would sit or rest in a cowering position, avoiding the light and unwilling to be handled, although he kept asking that the feet be held. This patient presented a picture as severe at least as the two fatal cases described above, and fear as to the outcome was felt.

Examination of the Nose and Sinuses.—In view of the nasal discharge, however, an examination of the nose was made by the nose and throat department, and an accumulation of crusts, as are seen in atrophic rhinitis, was found. Involvement of the maxillary antrum was suspected and examination confirmed the roentgenologic findings. A soft polypoid mass, three-eighths of an inch in diameter, was removed from the right antrum. Within a week after operation, a slight but distinct improvement was noted, and this continued until the time of discharge from the hospital. There was absolutely no recurrence. The child, while living in the poorest hygienic conditions, was repeatedly seen by the physician in charge who made regular reports to the clinic concerning his condition.

Case 6.—C. B. aged 3 years, male, was taken sick February, 1918, and admitted to the hospital in May, 1918.

Present Illness.—There is a history of some vague respiratory infection with progressive weakness and depression. During the early weeks of the disease he developed a skin eruption which was diagnosed as bullous impetigo. Some pustules came later. There then appeared the characteristic eruption on the fingers and to a less degree on the toes, the fingers being bluish-red, somewhat infiltrated and showing some desquamation. There were a few erythematous spots on the lobule of the ear and the cheeks showed a distinct and probably abnormal erythema. An eruption of the chest and the flanks was still present when the patient was first seen, and on the buttocks there were small, irregular erythematous spots from which small papules arose. These had been scratched quite a bit.

Physical Examination.—When the patient came to the hospital, examination showed distinct nasal obstruction (diphtheria-like bacilli on culture) and the tongue had the appearance of an early desquamating scarlet fever tongue. Muscular weakness was marked, but the reflexes were not only easily obtained, but were, if anything, exaggerated. The spleen just reached to the margin of the ribs and all lymph nodes were enlarged. The heart showed some increase in the diameter of dullness.

Laboratory Findings.—The Schick test was negative. Diphtheria antitoxin was given, but without benefit.

Subsequent History.—After the patient left the hospital, the toe nails came off and the finger nails became soft, but remained on the fingers. Improvement but not complete cure, as evidenced by the persistence of paresthesia and weakness, was reported seven months after the onset of the disease.

Case 7.—V. H., aged 10 months, female. This was the first case in a child under 1 year in the series. The patient was admitted in July, 1918, after one month's illness. One brother, 1½ years old, died of undoubtedly the same ailment in August, 1917. He buried his head in the pillow, his teeth fell out, and he had "boils" on the skin.

Present Illness.—The patient's trouble began with what was supposed to have been measles. There was a slight cold and the eyes became sore. The rash cleared up in a few days and appeared again the following week thicker than ever, the hands and feet being covered. With this second rash, and its accompanying temperature of 103 F., the condition of the child became progressively worse, with irritability, sweats, weakness and a very poor appetite. There were no digestive symptoms.

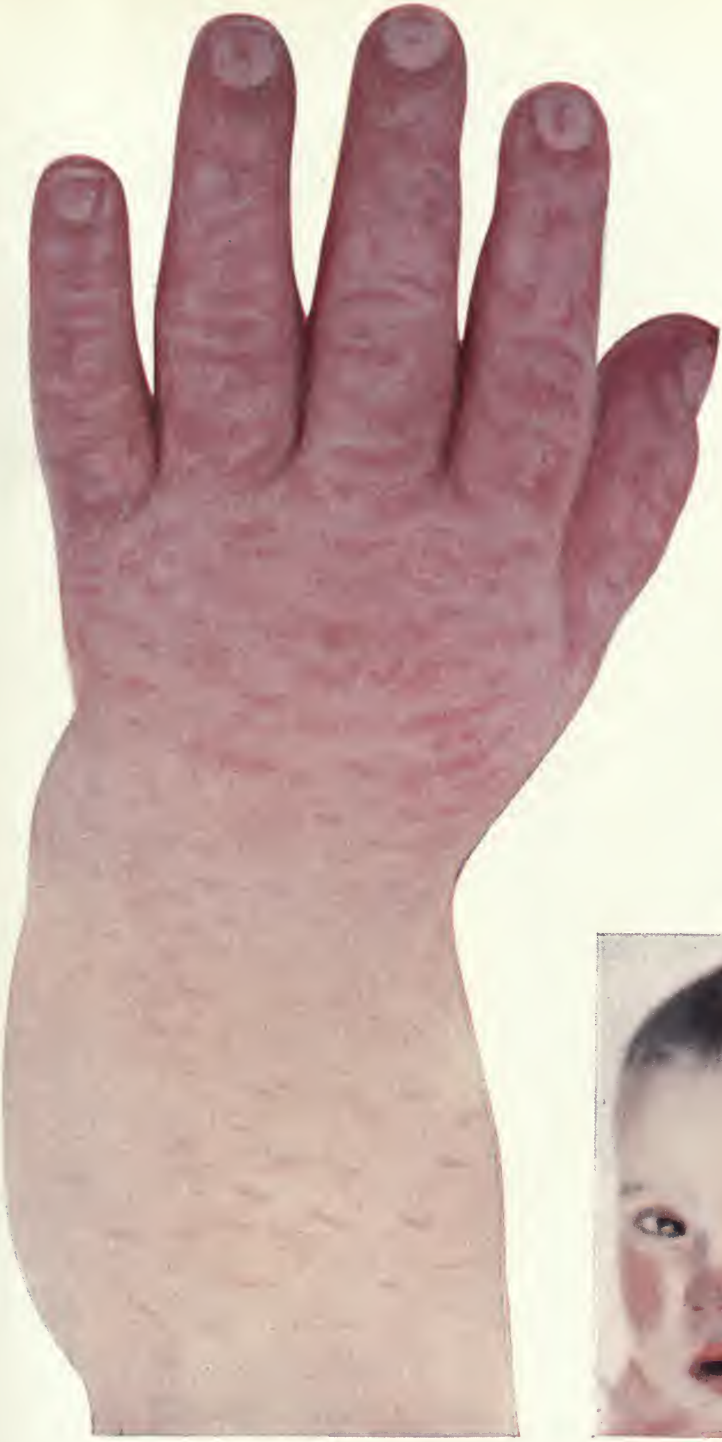

Figure 1

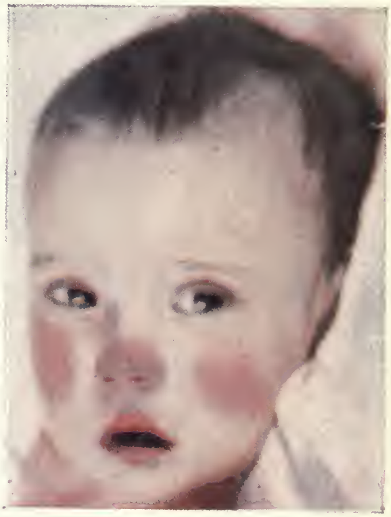

Figure 2

Fig. 1.—Case 8. Eruption on the hands with characteristic tendency to fading out toward the wrist.

Fig. 2.—Case 8. Involvement of cheeks and nose. This was the only case in which an eruption of any intensity appeared on the face.

Physical Examination.—On examination, anorexia, weakness, photophobia, and a skin eruption on the fingers and toes were the positive findings.

Laboratory Findings.—Leukocyte count, 16,400. Polymorphonuclears, 40 per cent. Nose and throat culture showed postive diphtheria-like bacilli. Schick test was negative.

Treatment.—After one month of observation, no improvement was noted, and tonsillectomy accordingly was performed Aug. 17, 1918. This patient left the hospital ten days later, still showing desquamation of the hands and feet.

Subsequent History.—Within one week from the time the child came home, she began to improve rapidly and made a complete recovery. When brought back to the hospital a short time after the operation she showed absolutely no signs of the disease.

Case 8.—M. K., aged 10 months, male, admitted to the hospital in March, 1919, after having been sick for four months. This baby had been breast fed.

Present Illness.—The trouble began one month after an attack of influenza. The symptoms that appeared were not different from those previously described.

Physical Examination.—The emaciation was very marked, amounting almost to a marasmus. The nose and the cheeks showed exaggerated redness, as seen in the illustration. Cervical glands were enlarged. The hands and feet were cold and the eruption tended to be macular in places, becoming confluent on the distal phalanges and macular toward the back of the hands. Reflexes were present. General wretchedness was intense.

Laboratory Findings.—Leukocyte count, 23,000. Polymorphonuclears, 72 per cent. Involution types of diphtheria-like bacilli were found. Acetone was present in the urine. No circulating diphtheria toxin was found in the blood.

Treatment.—As there was an element of distinct underfeeding in this case (acetonuria) this was corrected and the patient carefully observed for the effect of such treatment. Extracted antineuritic material was added to the milk and the diet bolstered. Moderate improvement was obtained. The special manifestations of the disease, however, seemed to be persistent in spite of the improvement in the general condition. After six weeks of observation and dietary treatment (no gavage) the tonsils and adenoids were removed and the nasal sinuses, which were found to contain pus, were drained. The improvement following the operation as far as the paresthesia and skin eruption was concerned seemed to be more distinct than that produced by the improved dietary: but a rapid cure (as in Case 7) was not achieved. A leukocyte count of 19,000 was present at the time the child left the hospital, indicating that the infection was still active. The child made a complete recovery, however, at home.

Case 9.—E. H., aged 22 months, male, was taken sick in January, 1919, and seen in the hospital in May, 1919. Subject to nasal discharge. Had influenza in October, 1918.

Present Illness.—In January, 1919, he began to become drowsy, his disposition changed, and a very distinct anorexia was noted. The hands and feet turned red and a rash came out on them which took two and one-half weeks for its complete development. Hands and feet were cold. He pulled his hair out in several places, but he never burrowed his head in the pillow or rubbed his hands. The eruption on the hands would clear up in part and then return again. When there was this local improvement, the general condition was also better. Desquamation of the fingers and toes followed the height of each eruption.

Laboratory Findings.—Leukocyte count, 7,400. Polymorphonuclears, 45 per cent. Acetone positive.

This was a moderately mild case with unmistakable lesions on the hands, but no grave systemic manifestations.

Treatment.—After admission to the hospital the child was fed a well selected diet which was followed by distinct improvement. In view of the persistence of the trouble, however, it was deemed advisable to have the tonsils and adenoids removed. The patient left the hospital cured and has not been ill since. It is impossible to say whether the operation produced any definite effect in this case.

Case 10.—J. S., aged 5 years, female; seen May 13, 1919. This little patient was the oldest in the series. Because of exposure to varicella, admission to the hospital was refused and the patient did not return. It was a mild but very definite case. Desquamation of the finger tips suggested a previous scarlet fever, but there was also very distinct erythema present and paresthesia, emaciation, irritability, anorexia and sweats.[24]

Case 11.—W. F., aged 2 years, female; admitted to the hospital Aug. 26, 1919. Family history negative. Breast fed for fifteen months. Feeding history was incomplete, except that it was known that the patient took more than a quart of milk a day. Patient had influenza in November, 1918.

Present Illness.—Present trouble began in February, 1919, with a cold and a cough. A rash broke out which lasted about two weeks and then cleared up. These rashes had been coming and going at intervals. Sweating was marked and there was much itching with the eruption.

This little patient did not show as much emaciation as did others in the series, but the paresthesia was quite marked both on the body and on the extremities. There was some purulent nasal discharge. There was also some swelling about the gums. The nasopharynx contained a considerable amount of purulent material which was yellow in color.

Besides hypertrichosis of the extremities, the hands were red from the webs of the fingers to the tips, the tinge increasing in intensity toward the tips. The palms had a rosy brown color, and appeared as if they had been violently rubbed on a piece of cloth. The redness did not fade on pressure. The hands were warm. On the feet a similar eruption was present, except that there was desquamation around the tips of the toes. Knee reflexes were somewhat diminished. This patient was in the hospital for a short time only and improved during that time. Further results not known.

Laboratory Findings.—Leukocyte count, 14,500. Polymorphonuclears, 65 per cent.; eosinophils, 2 per cent. Nasal culture showed a few diphtheroids. Urine was negative.

Case 12.—R. G., aged 1 year, male, was first seen Feb. 24, 1920, being the first of seven cases of the first half of 1920. This was a breast fed baby, whose mother apparently had a diet adequate in every respect, as determined by careful questioning.

Present Illness.—The onset of the trouble was early in January, 1920, seven weeks before the examination and was without definite assignable cause, although the baby was cutting teeth at the time. The child became unusually irritable and restless, especially at night. When it did sleep, it would double up and burrow its head in the pillow. With the loss of appetite the weight grew less. Frequent body sweats attracted the attention of the parents. The child previously had made attempts to stand, but became so weak that this was impossible. Itching of the hands and feet was marked and there was some desquamation on the body. This desquamation, as well as a slight reddening of the fingers and toes, appeared four weeks after the assigned onset of the disease.

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[24] This patient was later seen by another physician who has written me that for several days the child had frequent convulsions and between these was practically in coma. On the basis of these symptoms he concluded that the child was suffering with lethargic encephalitis. If this assumption is correct, it is another bit of circumstantial evidence in favor of the relationship of "acrodynia" and influenza.

He found the leukocyte count to range from 17,000 to 20,000 with from 73 to 80 per cent. polymorphonuclears. This increase in white cells has been referred to in the body of the article.

Examination showed a most irritable and uncomfortable baby, who, while still in a fair state of nutrition, had undoubtedly lost considerable weight. There was no falling out of the hair. The gums were a little red where the new teeth were beginning to come through, and a pyorrhea-like deposit was seen on the already erupted teeth which were otherwise in good condition. The tonsils were large and moderately congested, being of the type in which the anterior pillar covers a large part of the gland.

On the thorax there was a definite macular eruption. There seemed to be some increase in the lateral diameter of the heart. The spleen was not enlarged. On the hands were seen the usual distinct small papules lying in an erythematous base. These patches of affected skin were close together, but not confluent. They grew less in number toward the hand and wrist. There was a moderate amount of cyanosis and edema of the hands. The feet were similarly involved. Desquamation at the finger tips was present, slight but distinct. Reflexes at the knee were slightly diminished.

Case 13.—D. Y., aged 3 years, female, was admitted to the hospital Feb. 13, 1920. The family history was negative. This was a breast fed baby which after being weaned was placed on table diet consisting of the usual foods but with few vegetables.

Present Illness.—The onset of the trouble was in October, 1919, and seemed to begin with paresthesia of the legs and feet—the child always wishing to take off its shoes and stockings because of the distress. A month later the eruption was noted on the hands, feet, abdomen and later on the back. This eruption would disappear for a week and then break out again, each followed with desquamation. The rash on the abdomen was more constant. In the last month she became much weaker and gradually lost the power of feeding herself and standing.

Physical Examination.—Examination showed a very emaciated child, lying in a partial stupor. The lungs showed distinct involvement in the form of consolidation and râles which, with the positive intradermal test, were assumed to be tubercular in character. The hands and feet showed the characteristic associated papular eruption on an erythematous base. The finger tips were desquamating, and coldness of the extremities was marked. There was some eruption and some pigmented spots on the thorax and abdomen. Many scratch marks were present. Reflexes at the knees and ankles were lost.

Course of Disease.—The child was evidently critically ill and death, which followed in two days, was not unexpected. The necropsy showed the changes previously described.

Laboratory Findings.—Leukocyte count, 11,000. Polymorphonuclears, 61 per cent. Intradermal test with tuberculin, 1:10,000, positive. Urine showed acetone, 1 plus. Diacetic acid, faint trace. Pus cells, 7,200 per c.mm. Nasal culture showed diphtheria-like bacilli usually found in these cases.

Case 14.—L. S., aged 22 months, female, was first seen March 29, 1920. The family history was negative. This child had been breast fed for nineteen months and in addition had recently been given "almost anything" from the table, including one quart of milk a day.

Present Illness.—Present trouble began in January, 1920, and consisted in a breaking out all over the body, which lasted only one day. In February, another breaking out was noticed and this has been present since. Sweating was very marked and the weakness great. Appetite was fair.

Physical Examination.—Examination showed the usual emaciation and loss of subcutaneous fat, especially in the thighs and groins. The hair was extremely dry and came out easily and there were spots where it was quite gone off. There was a slight discharge from the right ear. Of the upper teeth all had fallen out, except the two upper premolars and one central incisor which were at this time very loose. The lower teeth were present but also loose. Pyorrhea was marked. There were purulent droppings from the posterior nasopharynx. The skin rash was scarlatiniform on the chest and on the palms of the hands there were excoriations, while ulcers were present on the three fingers of the right hand and on the index finger of the left, due probably to scratching or chewing. Reflexes at the elbow were present but absent at the knees. Abdominal reflexes were diminished and there was some loss of cutaneous sensibility to the prick of a pin.

Laboratory Findings.—Leukocyte count, 16,200. Polymorphonuclears, 65 per cent.; eosinophils, 2 per cent.; urine showed 250 pus cells per c.mm. Nose culture showed the usual diphtheria-like polar staining bacilli. Spinal puncture showed 20 pus cells per c.mm. Noguchi, a trace.

CASE 15.—H. A., aged 2 years, female, was admitted to the hospital, April 7, 1920. The family history showed that there was a distinct tendency to diabetes. This child was breast fed and subsequently received a very generous diet although it seemed as if the child did not like milk and eggs.

Present Illness.—Present trouble began about Christmas, 1919, with cough and glandular swelling. Respiratory infection was present now and again up to the time of admission (April 7), there being otitis media March 23. Emaciation, weakness and sweating had been marked. The child, who could formerly walk, gradually lost its power of either standing or sitting. There were no marked skin eruptions, although red spots about the size of a dollar came out on the forehead, hands and face.

Emaciation was distinct with very marked loss of subcutaneous fat. The child was apathetic, weak and uncomfortable. The extremities were cold. A cough was present. There was paresthesia but no eruption on the extremities, although the finger tips were cyanotic. Fleeting erythematous spots were noted on the body. The tongue was red. There was some deposit about the teeth but no decay. The reflexes were absent. The child absolutely refused to drink milk and it was necessary to resort to the stomach tube. In spite of the diminished feeding polyuria was present. In the colon a chain of fecal masses was felt. This patient made a quick recovery under forced feeding and left the hospital in excellent condition, being then able to stand and walk. The tendency to frequent urination, itching of the hands and anorexia disappeared.

Laboratory Findings.—Leukocyte count, 22,400. Polymorphonuclears, 75 per cent.; basophils, 4 per cent.; urine showed trace of acetone. Pus, 30 cells. Lumbar puncture showed Noguchi 1 plus with pus cells, 10 per c.mm. Nose culture showed an almost pure culture of diphtheria-like bacilli.

CASE 16.—H. R., aged 2 years, female, was admitted to the hospital May 5, 1920. The baby had been breast fed for nine months and was then given a diet which seems to have been "complete."

Present Illness.—Following an attack of influenza in March, 1920, there was a skin rash which was scarlatiniform for the hands peeled, and a presumptive diagnosis of scarlet fever was made by the doctor at home. Weakness, emaciation, pulling at the hair and burrowing the head in the pillow were prominent symptoms. The child felt as though it wanted to urinate every ten minutes but passed only a small amount each time. She gradually lost the power of walking.

Physical Examination.—On examination the child did not give the general appearance of emaciation but the weight was less than that of a chilld 1 year old. The distress was not marked as in more severe cases, but the listlessness was definite. The patient did not move around nor did she stand. She pulled her hair and rubbed her hands. There was a slight erythema of the finger tips and some desquamation. The extremities were cold. The reflexes at the knees were definitely absent.

Laboratory Findings.—Leukocyte count, 16,600. Nose culture showed diphtheria-like bacilli. Urine showed acetone, 2 plus. Pus, 400 cells per c.mm.

Treatment.—After a month of dietary treatment in the hospital, the improvement was only slight and nasal operation seemed advisable. This consisted in removal of the tonsils and adenoids, and puncture of the nasal sinuses in which latter pus was found. The nasal discharge became so profuse that more complete nasal drainage was necessary and when this was secured the child's improvement seemed quite definite. This patient is still under observation.

Case 17.—F. J., aged 8 months, female, was admitted to the hospital, June 1, 1920. The baby had been breast fed up to the time of admission.

Present Illness.—Present trouble began in April with diarrhea, the stools being very watery. Itchiness and general distress followed very shortly after, irritability being marked. The baby chewed its hands and pulled at its hair. Anorexia was definite.

Physical Examination.—From the description of the baby's symptoms, given over the telephone, a presumptive diagnosis was made which was verified when the child was seen in the hospital the following week. At this time it was extremely uncomfortable, had lost weight and strength, and had a temperature of 103 F. Over the end phalanges there was an erythema and the toes were similarly involved. The hands and feet were very cold. The body was quite free of eruption. A rather surprising amount of postnasal mucopurulent droppings was seen; these caused a very distressing cough.

Laboratory Findings.—Leukocyte count, 9,000 (on admission). Urine showed pus cells as high as 700 per c.mm. Acetone was present at times. Diphtheria-like bacilli were found in the nose.

Course of Disease.—A recurrence of the enterocolitis (from ten to twenty stools a day) took place a week after the baby's entrance to the hospital, and with this a pneumonia involving the whole of the right lung developed. The irritation of the fingers became so extreme with the onset of the pneumonia that the baby actually bit into them and made it necessary for the hands to be bandaged and tied to the bed. This patient is still under observation.

It is very probable that while diarrhea was the first symptom noted, there was a respiratory infection present at that time. This assumption is strengthened by the fact that "summer influenza" was prevalent in the region from which the patient came.[24]

A STUDY OF THE BLOOD AND ITS CIRCULATION IN NORMAL INFANTS AND IN INFANTS SUFFERING FROM CHRONIC NUTRITIONAL DISTURBANCES *

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INTRODUCTION

The study of the nutritional disorders of infants has followed the development of medicine as a whole. The early Vienna school referred all disturbances to pathologic changes in the gastro-intestinal tract and classified the diseases anatomically. For example, there was gastritis, enteritis and colitis. When the knowledge of bacteriology became more developed, the bacteriologic factor was actively discussed and studied without leading to a much clearer conception of these disorders. It was not until chemistry became fully developed that more light was thrown on the nutritional disorders. It was, however, soon felt that even chemistry could not supply all the answers wanted and, therefore, the study of the child itself was emphasized. The constitutional factor was brought to the physician's attention. This point of view in pediatrics with Czerny as its chief exponent has never, so far as I can see, been completely accepted in America.

There is a growing tendency to consider that physical as well as chemical factors must be studied in order to reach a full understanding of the changes occurring in the body in the course of nutritional disturbances. At Dr. Marriott's suggestion I took up this question for further investigation.

WHAT CHANGES TAKE PLACE IN THE WATER METABOLISM OF INFANTS DURING NUTRITIONAL DISORDERS

Freund[1] was, so far as I know, the first to draw attention to the fact that the up and down line of an artificially fed infant's weight curve can only be explained by the ever changing water content of the body and not by the variable content of dry substances.

The water content of the body is not constant, in fact, it varies much, and the younger the individual the greater the variation.

It is influenced by two main physiologic factors:

1. The age of the individual.
2. The character of the food.

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[1] Freund: Jahrb. f. Kinderh. **59**:421, 1904.

Besides these two factors must be mentioned diseases which influence the water content by increase or decrease of the body excretions.

As far as the age is concerned, Bezold[2] in 1857 studied this question thoroughly and came to the conclusion that there was a decrease of the water content and volatile constituents from the embryonic period to the height of full development. This fundamental work done sixty-three years ago gives us what we know today about this question. Nothing essentially new has been added.

The other main factor is the feeding. The importance of this has been noted by Bischoff and Voit.[3] In 1860 they performed an experiment on a dog fed exclusively on bread for a period of 41 days. They found that although the nitrogen loss corresponded to 3,713 gm. of muscle, the animal lost only 351 gm. in weight, and concluded that water retention must have taken place. Further, Bischoff and Voit[4] fed cats exclusively with bread and found the water content of the brain and muscles to be from 3 to 4 per cent. higher than in control cats fed with mixed food. According to Zuntz, Loewy, Muller and Caspari[5] this is due to the fact that when glycogen is stored in the body it takes with it three times its weight of water. Rubner's[6] statement that the water content in the body depends exclusively on the simultaneous fat content has been disproved by different authors. Steinitz,[7] Hoesslin,[8] Forster[9] and Chaniewski[10] all showed that the water and fat content of different organs are not always inversely proportional to each other. Weigert's[11] work on dogs in 1905 shows very plainly that the water content of the body depends not only on variations in the fat content but also on the amount of fat free substances present.

The experimental work done so far seems to show there are two physiologic factors which determine the water content of the body, viz.: (1) the age; (2) the feeding.

In passing to a consideration of the infant's organism it is clear that in order to get an idea of the water content the ideal way would be to make a complete study of all the organs which are especially known to be the water repositories. Such a procedure is, of course, impossible during life. The only organ which is available for investigation is the blood. Many examinations of this organ have been made.

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[2] Bezold: Ztschr. f. Wissenschaftl. Zoologie **8**:1857 (according to Lederer[28]).

[3] Bischoff and Voit: Die Gesetze der Ernährung des Fleischfressers, 1860.

[4] Bischoff and Voit: Hermann's Handbuch der Physiologie **6**:347.

[5] Zuntz, Loewy, Muller and Caspari: Hohenklima und Bergwanderungen, 1906, p. 114.

[6] Rubner: Lehrbuch der Hygiene, 1900, p. 440.

[7] Steinitz: Jahrb. f. Kinderh. **59**:447, 1904.

[8] Hoesslin: Deutsch. Arch. f. Klin. Med. **33**:600, 1883.

[9] Forster: Ztschr. f. Biol. **12**:448, 1876.

[10] Chaniewski: Ztschr. f. Biol. **20**:448, 1884.

[11] Weigert: Jahrb. f. Kinderh. **61**:179, 1905.

Since the work of Audral and Gavaret[12] in 1842 an immense amount of literature on this subject has appeared. Most of the work, however, has been performed on adults and only during the last ten years have pediatricians paid especial attention to the topic.

The first question which arises is whether or not it is possible to draw conclusions concerning the water content of the body, as a whole, from an examination of the blood alone.

For a long time it has been believed that the blood did not change its concentration at all, that under different conditions it tended to keep its composition constant and that when necessary water from the different water depots could be drawn upon to supply any deficit. Magnus,[13] for instance, thought so and with him Plehn[14] and Engels.[15] Panum[16] held a different opinion and Tobler[17] was able to demonstrate in his experiments on dogs, on which he produced a water loss by diarrhea, that the water loss in the blood amounted to several per cent. Grawitz,[18] who must be considered as an authority on this question, has also observed a marked concentration of the blood as a result of water loss from various causes. At the same time, he called attention to the fact that these changes often take place so quickly that they may be overlooked when the examinations are made too late. He further states that the blood should not be considered as an isolated organ of invariable volume but as part of the lymphatic system with which it is intimately associated.

In the last ten years several studies have been made on the water content of infants' blood. The main purpose has been to determine the relationship of variations in body weight to fluctuating water contents in the blood and thereby in the whole organism, and especially to follow the water metabolism during acute diarrhea and vomiting. Various methods have been used by different authors. The methods have been: (1) specific gravity determinations; (2) direct determination of dry substances; (3) chemical determination of protein; (4) freezing point lowering; (5) conductivity determinations, and (6) viscosity. These methods either require so much blood or are so time consuming that they are not well adapted for blood examinations on infants who can stand but little loss of blood, especially when the determinations have to be done daily. These difficulties are overcome by the use of the refractometric method first used by Strubell,[19] i. e., the determination of the protein concentration of the blood by refraction. It has been shown by earlier workers that the refractive index of the blood serum may be regarded as a function of the protein. It is, of course, only an approximate estimation because the angle of refraction is not affected by protein alone. Protein does, however, change the angle of refraction much more than the other solid constituents of the blood serum. Salts and other substances which have to be considered, show, with some exceptions, a rather constant concentration and also constant refractometric value which has to be subtracted. The error due to changes of these substances does not exceed 0.3 per cent. of the calculated protein content. The refractometric method gives a good approximate result though no conclusions should be drawn from very small changes. In regard to the actual water content of the blood this method gives us just what we want to know, because changes in the water content have most effect on the relative protein content of the blood serum while the salts, on account of the constant osmotic pressure of the blood, are usually present in fairly constant amounts.

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[12] Audral and Gavaret: Ann. d. Chem. et Physiol. **55**:1842. (According to Lust.[21])

[13] Magnus: Archiv. f. Exp. Path. und Pharmak., 1900, XLIV, 68.

[14] Plehn: Deutsch. Arch. f. Klin. Med. **91**:1, 1907.

[15] Engels: Arch. f. Exp. Path. u. Pharmak. **51**:346, 1904.

[16] Panum: Virchows Arch. f. path. Anat. **29**:241.

[17] Tobler: According to Lust, note 21.

[18] Grawitz: Klinische Pathologie des Blutes, Chapt. VI. "Das Gesamtblut ist nicht als ein abgeschlossenes Organ von invariablen Volumen anzusehen, sondern steht durch das die Kapillaren umgebenen System von Lymphräumen in ununterbrochenen Austausch von Stoffen mit den Flüssigkeiten der Gewebe."

The first work of any importance performed on infants' blood was done in 1909 by Emil Reiss,[20] who made use of the refractometric method. He is, as far as I know, the only one who has examined normal infants at different ages but apparently he examined one infant of each age. He found a constant increase from birth up to the tenth or twelfth month when the concentration reaches that of the adult. Furthermore, he examined nineteen cases of different gastro-intestinal disturbances in which he found a special relationship between the weight curve and the protein concentration of the blood. Most of his patients were suffering from acute diarrhea or vomiting, and showed a high concentration of the blood, which under treatment fell to normal.

In 1911 Lust,[21] using the method of determining the dry substances in the blood, obtained results very similar to those of Reiss. His material consisted of twenty cases and one of his conclusions was that in the chronic intestinal disturbances the water content of the blood does not differ from that of the blood of normal infants. Behrend and Tezner [22] examined the blood of infants with alimentary weight changes in regard to refraction, viscosity, freezing point lowering and conductivity but found no special relationship between the changes in the blood concentration and the weight. In 1914 Lederer [23] published a paper on the same subject. His method was the determination of the total dry substances of the blood by weighing on Kuhlmann's scale. He examined five normal infants and thirteen infants with chronic intestinal disturbances and found in most instances a high water content of the blood.

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[19] Strubell: Deutsch. Arch. f. klin. Med. **69**:521, 1901.

[20] Reiss: Jahrb. f. Kinderh. **70**:311, 1909.

[21] Lust: Jahrb. f. Kinderh. **73**:85, 1911.

Recently Marriott and Perkins,[24] using the refractometric method, found a high concentration of the blood in acute diarrhea (Fig. 1) and a low protein concentration in the chronic nutritional disturbances (athrepsia).

As a summary of the literature it may be stated that most authors have found the acute nutritional disturbances with diarrhea and vomiting usually are followed by a concentration of the blood. Only in the discussion of chronic intestinal disturbances do the opinions differ markedly. Since the cases which have been studied are very few, it was considered desirable to obtain a greater number of observations.

PART I. EXAMINATION OF INFANTS

The blood concentration of normal infants and the physiologic variations have, as I have mentioned, been examined by Reiss. I have collected additional material on this point. The blood examined was taken from the infant's heel without any pressure two or three hours after meals. Earlier work has shown the influence of food intake on blood concentration. Schmaltz [25] showed, with the capillary pyknometer, that the specific gravity usually drops after meals and returns to normal half an hour after the last meal. Hammerschlag [26] showed with the same method that the difference could be noted in from fifteen to thirty-five minutes after meals, but this had disappeared in from forty-five minutes to one hour after the meal. Lust [21] found that fluid intake raised the water content of the blood as much as from 0.2 to 0.4 per cent. In view of the foregoing it would seem likely that if blood were taken from two to three hours after meals, the influence of the meal would be eliminated. The results appear in Table 1.

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[22] Behrend and Tezner: Monatschr. f. Kinderh. **10**:212, 1911.

[23] Lederer: Ztschr. f. Kinderh. **10**:365, 1914.

[24] Marriott: Am. J. Dis. Child. **20**: (Dec.) 1920 (to be published).

[25] Schmaltz: Deutsch. Arch. f. klin. Med. **47**:145, 1891.

[26] Hammerschlag: Ztschr. f. klin. Med. **20**:444, 1892.

TABLE 1.—The Blood Protein of Normal Infants

Age	No. of Infants Examined	Average Protein Percentage	Age	No. of Infants Examined	Average Protein Percentage
1 day	14	6.25	3 months	1	6.06
2 days	12	5.8	3½ months	2	6.33
3 days	12	6.33	4 months	2	6.55
4 days	9	6.63	4½ months	3	6.35
5 days	13	6.59	5 months	4	6.90
6 days	9	6.25	5½ months	1	6.12
7 days	8	6.83	6 months	2	6.34
8 days	4	6.27	8 months	1	6.12
9 days	7	6.33	11 months	1	6.87
10 days	3	6.19	13 months	3	7.00
11 days	4	6.03	13½ months	1	7.63
12 days	4	6.26	15 months	1	7.42
13 days	3	6.47	16 months	3	7.63
14 days	3	5.90	17 months	3	7.63
16 days	1	6.12	20 months	1	8.71
1 months	3	6.29	2 years	2	7.86
1½ months	3	6.28	2⅓ years	1	8.06
2 months	2	6.32			

It will be seen that the protein content during infancy varies from 6 to 6.5 per cent. and remains at this level until the tenth or eleventh month, when it begins to rise. By the fifteenth month it has reached the adult level.

The results are expressed graphically in Figure 1. (For purposes of comparison the results obtained by Marriott and Perkins on infants suffering from acute diarrhea with toxic symptoms are included in the chart).

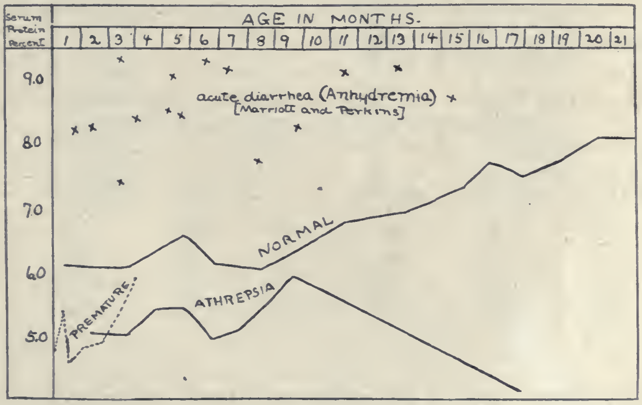

Figure 1

We see here the influence of one of the factors mentioned in the beginning of this paper, namely, the age. The old, well known fact is once more stated: *The younger organism contains relatively more water than the mature organism.*

If we could follow the baby back into intra-uterine life we would, according to Bezold,[2] find a still higher water content. This explains very easily the high water content of premature infants which has been found as may be seen in Table 2. Premature infants do not acquire a normal water content before 3 months of age (Curve 1).

TABLE 2.—Blood Protein of Premature Infants

Number	Age	Average Protein Percentage	Number	Age	Average Protein Percentage
1	1 day	4.91	13	3 weeks	5.03
2	1 day	4.16	14	5 weeks	4.16
3	2 days	3.94	15	5 weeks	5.42
4	3 days	5.13	16	6 weeks	4.47
5	3 days	5.13	17	6 weeks	4.42
6	1 week	5.78	18	7 weeks	5.03
7	2 weeks	5.05	19	7 weeks	5.23
8	2 weeks	5.68	20	9 weeks	5.68
9	2 weeks	5.68	21	10 weeks	5.90
10	3 weeks	4.59	22	3 months	6.34
11	3 weeks	4.49	23	3¼ months	6.77
12	3 weeks	4.26			

These tables serve as confirmation of Bezold's conclusions,

As far as the physiologic daily changes are concerned, there has been little done. Rusz,[27] who examined ten infants, found the protein content (refractometric method) to decrease steadily during the day and found the lowest value in the evening. This he believes to be the result of the fluid intake during the day. Furthermore, he found such a high difference between the morning and evening figures that he believes no conclusions can be drawn regarding pathologic changes. My findings do not agree with his.

TABLE 3.—Blood Protein of Infants Showing the Results of Several Examinations Upon the Same Day

No.	8 a.m. per Cent.	12 noon per Cent.	8 p.m. per Cent.	No.	8 a.m. per Cent.	12 noon per Cent.	8 p.m. per Cent.
1	7.63	8.28	8.38	8	6.34	6.22	6.34
2	6.55	6.98	6.77	9	6.34	6.00	6.55
3	4.47	4.26	4.25	10	5.90	6.00	6.65
4	6.12	5.47	5.90	11	8.25	7.50	7.52
5	6.34	6.22	6.55	12	5.78	5.90	5.78
6	6.87	7.08	7.10	13	7.08	7.20	6.55
7	7.85	7.85	8.28				

Table 3 shows that of the thirteen infants examined six showed the highest protein in the evening, two no change, three lowest in the middle of the day and only two lowest in the evening. And, furthermore, the daily difference never exceeded 0.75 per cent. It is thus seen that the daily physiologic changes are so slight that it is justifiable to draw conclusions from larger deviations in pathologic conditions.

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[27] Rusz: Monatschr. f. Kinderh. **10**:360, 1911.

So far as chronic nutritional disturbances are concerned, as has been mentioned before, different authors' results differ very much. It was my special purpose to examine athreptic infants.

"Athrepsia," "pedatrophy" and "dekomposition" are all names used to indicate the last stages of a chronic nutritional disturbance. The picture is very well known to the pediatrician. We are dealing here with infants who usually have passed through several acute intestinal disturbances and at last have gone over into the athreptic stage and show the characteristic picture of athrepsia with gray, pale skin covering a practically fatless body of which the bones, head and the stomach are the predominating parts. The hard, often rachitic bones fill the skin, which on account of the disappearance of fat from the subcutaneous tissue, appears too large. The lines of the head and face bones are marked, the eyes are deep and the cheeks fallen in. On this account the terms "Greisengesicht" or "Face de Voltaire" are used. In Table 4 and in Figure 1 are shown results obtained on the blood serum of a number of these infants.

TABLE 4.—Blood Protein of Athreptic Infants

Number	Age	Protein Percentage	Number	Age	Protein Percentage
1	1 month	5.78	20	3 months	5.68
2	1 month	5.13	21	3 months	5.47
3	1 month	5.30	22	4 months	5.31
4	1½ months	4.59	23	4 months	5.90
5	1½ months	5.68	24	4 months	5.57
6	1½ months	5.57	25	4 months	5.90
7	1½ months	5.38	26	4½ months	5.57
8	2 months	4.37	27	4½ months	5.49
9	2 months	5.68	28	4½ months	5.30
10	2 months	5.31	29	5 months	5.47
11	2 months	5.90	30	5 months	5.25
12	2 months	4.69	31	5½ months	5.80
13	2½ months	4.69	32	5½ months	5.57
14	2½ months	4.59	33	6 months	5.25
15	2½ months	4.81	34	6 months	4.67
16	3 months	5.78	35	7 months	5.32
17	3 months	4.91	36	9 months	6.16
18	3 months	5.68	37	18 months	3.94
19	3 months	5.78			

By comparison with Table 1 it will be seen that the average protein content of the serum of these infants is distinctly lower than that of normal infants. Why do these athreptic infants have a higher water content of the blood than normal infants of the same age? 1. Is this a direct result of the bad feeding usually preceding the emaciation, or, (2) is it dependent on the development of the athrepsia itself, or (3) is it to be regarded as an individual attribute, that is, belonging to the infant's constitution?

In regard to the first question, it is to be noted that 80 per cent. of these athreptic infants whose blood has been examined have been fed entirely or almost entirely on sweetened condensed milk mixtures.

Without going into detail here, it will be seen at once by looking at Table 5 that it is a feeding with a very high sugar percentage and low fat, protein and salt per centage. It is overfeeding with carbohydrates and if diarrhea and vomiting are not the immediate results the infants after a while often stop gaining and a nutritional disturbance of the "mehlnahrschaden" type develops which at last leads to athrepsia. In reference to what has been said before in this paper relative to the influence of food on the water metabolism of the body, I will only add that Franke and Stolte [28] in their studies of liver substance from infants suffering from "mehlnährschaden" found an abnormally high water and salt content.

TABLE 5.—COMPOSITION OF SWEETENED CONDENSED MILK (EAGLE BRAND) *

	Condensed Milk, per Cent.	With 6 Parts Water Added, per Cent.	With 12 Parts Water Added, per Cent.	With 18 Parts Water Added, per Cent.
Fat	9.61	1.37	0.73	0.50
Protein	8.01	1.14	0.61	0.42
Sugar (cane, 42.91; milk, 12.03)	54.94	7.89	4.75	2.90
Salts	1.78	0.25	0.13	0.09
Water	25.66	89.35	94.28	96.09

* Holt: "Diseases of Infancy and Childhood," p. 158.

Furthermore, experimentally it has been found that such a feeding has not only a temporary effect on the organism but exerts a lasting effect on the chemical processes of the organism even after the feeding is changed. Several of these infants were followed for months with no change in the blood picture even though the feeding for a long time had been a proper one. One infant who was discharged while gaining but with low protein content of the blood was admitted again two months later on account of diphtheria and showed just the same blood picture.

As regards the second possibility, reference may be made to Ohlmüller's [29] work. He found by analysis of the organs from infants that a normal child contains 60 per cent. water and 40 per cent. solid material, while an athreptic one contains 74 per cent. water and only 24 per cent. solids, a fact which he ascribed to the loss of fat in athreptic infants.

The process could easily be considered as a lack of power on the part of the organism to build up its blood protein.

As far as the third possibility, the individual or the constitutional factor, is concerned, it is well known that Czerny [30] requires a constitutional factor for the development of athrepsia. That these infants either (1) have an exudative diathesis, or (2) are children of neuropathic parents with an extreme irritability of the nervous system of the intestinal tract, or, (3) are children with hydropic constitution who show differences in water and salt retention from normal children. If this were a matter of constitution the constant high water content even after changing the food could be easily explained. On the other hand, we should not expect such a change as is seen in the following cases.

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[28] Frank and Stolte: Jahrb. f. Kinderh. **78**:167, 1913.
[29] Ohlmüller: Ztschr. f. Biol. **18**:78, 1882.
[30] Czerny: Am. J. Dis. Child. **3**:171 (Feb.) 1912.

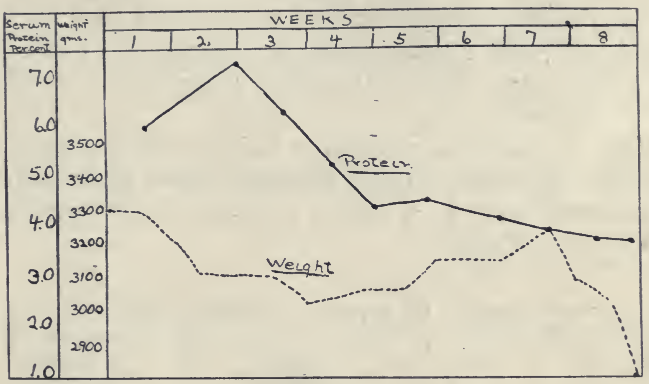

Figure 2

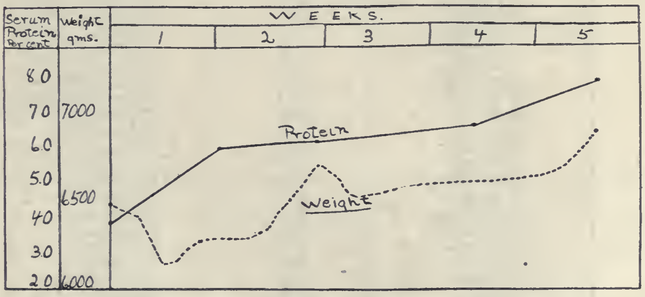

Figure 3

Figure 2 shows the findings from a patient admitted on account of gonococcus infection of the eyes. The blood protein on admission was normal, 6 per cent. The baby developed an ileocolitis. The blood protein went up to 7.20 per cent. Diarrhea stopped and blood protein went down to nearly normal but the baby would not gain and went over in an athreptic stage with drop of protein to 4.37 per cent.

Figure 3 shows the results from an infant who was recovering from a nutritional disturbance.

After having had indigestion for three months the child was admitted very emaciated, a typical picture of athrepsia with blood protein 3.94 per cent. In the hospital the child recovered very rapidly. There was an increase in the protein content of the blood, which was 8.06 per cent. when the child was discharged, in excellent condition, after having been fed on the high caloric whole lactic acid milk especially fitted for these athreptic infants (Marriott [31]).

Both cases seem to indicate that there is a lack of power on the part of the organism to build up protein in the low athreptic stage.

As both infants, however, before admission had been fed on sweetened condensed milk, the first mentioned factor, the food, also plays a part in those cases even if the blood protein in the first case was normal on admission.

In order to determine whether or not the blood picture found is characteristic of the condition of athrepsia I have examined the blood of patients suffering from a variety of other clinical conditions. The results appear in Table 6.

TABLE 6.—Blood Protein of Infants Suffering From Various Diseases

Number	Age	Protein Percentage	Diseases
1	4 months	5.90	Exudative diathesis
2	4 months	5.90	Harelip
3	5 months	6.22	Bronchopneumonia
5	6 months	6.55	Bronchitis
6	6 months	4.81	Exudative diathesis
7	6 months	6.77	Malaria
9	7 months	7.42	Tetany
10	7 months	7.42	Tetany
12	9 months	7.56	Tuberculosis
13	10 months	7.52	Otitis media
14	10 months	6.34	Bronchopneumonia; anemia
15	13 months	8.06	Epidemic meningitis
16	13 months	7.63	Tuberculosis
17	13 months	7.20	Congenital syphilis
18	14 months	8.49	Congenital syphilis
19	14 months	8.0	Bronchitis
20	15 months	7.95	Tuberculosis
21	15 months	5.78	Pneumonia
22	16 months	5.30	Pneumonia
23	18 months	8.00	Encephalitis
24	20 months	8.06	Encephalitis
25	21 months	7.00	Tuberculosis
26	2 years	8.12	Rickets
27	2 years	5.90	Rickets
28	2 years	7.20	Exudative diathesis
29	2 years	7.00	Congenital syphilis
30	3 years	8.36	Acidosis, postoperative
31	7 years	6.45	Nephritis
33	1 year	7.52	Bronchopneumonia

It is seen that with the exception of nephritis and exudative diathesis the figures do not differ much from those of normal infants. It is a known fact that in these two conditions there is a retention of water in the blood and tissues.

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[31] Marriott: J. A. M. A. **73**:1173 (Oct. 18) 1919.

IN WHAT RELATIONSHIP DO THESE BLOOD CHANGES STAND TO THE SYMPTOMATOLOGY OF NUTRITIONAL DISTURBANCES

The similarity between the water content of premature and of athreptic infants is very striking (Tables 2 and 5). We know that morbidity and mortality decrease from birth to full development, and that both mortality and morbidity of premature infants are still higher than among babies born at term. When we remember that the water content of the blood also steadily decreases from prematurity to the time of full development it seems that we cannot help but place these two facts in relation to each other. We are well acquainted with the low immunity of the premature infant and just as well acquainted with the different and often multiple infections which often form the most prominent feature in the picture of athrepsia. So prominent indeed that there was a time in pediatrics when the infections, especially otitis media with intoxication from bacterial products, were considered as a cause and not as one of the symptoms of athrepsia. The high water content of the premature and athreptic infants might be considered one of the factors which explains their low immunity.

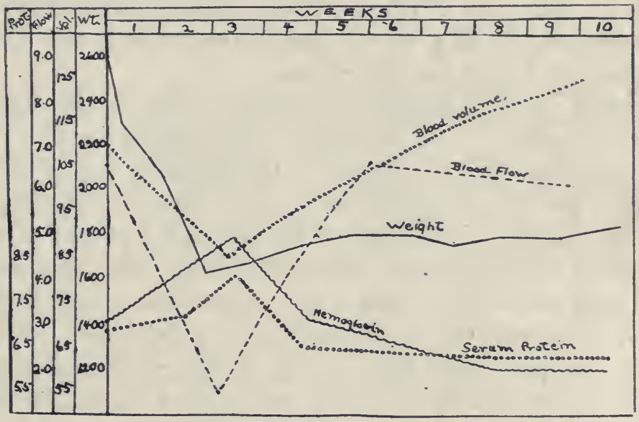

Figure 4

Experimental work has confirmed the finding of the low immunity of hydrated tissues (Schultz [32]).

Weigert's work [33] emphasized the importance of the water content of the medium for growth of different bacilli; he found further [34] that pigs fattened on high carbohydrate feeding whose tissues were in a state of hydration, showed an exceptionally low resistance to tuberculosis as compared with normal pigs or those fed on mixtures predominating in fat content. Thomas [35] and Hornemann [36] corroborated these findings.

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[32] Schlutz: Am. J. Dis. Child. **16**:135 (Aug.) 1918.
[33] Weigert: Centrabl. f. Bakteriol. **36**:112, 1904.
[34] Weigert: Berl. klin. Wchnschr. **44**:1209, 1907.

THE BLOOD CIRCULATION IN INFANTS IN HEALTH AND DISEASE (ATHREPSIA)

Until recently observations on the rate of blood flow have been made almost exclusively in the laboratory since there were no known methods fitted for clinical application.

Two methods have been in general use. One, Ludwig's "Strohmuhr" or various modifications of this; the other, which does not involve any interference with the blood vessels, the plethysmographic method of Brodie. This latter method has long been known but it has found little application to clinical work. Even the application of the plethysmographic method to the arm (Hewlett and von Zwaluwenburg [37]) has not found any general use.

A method easily adaptable to clinical work is the calorimetric method of Stewart.[38] The principle of this method is: that providing the blood passing from the thorax to the hands or feet is of constant temperature the rate at which heat is distributed from the hands or feet will be directly proportional to the rate of movement of the blood through these parts. Stewart found that hands, and, to a less degree the feet, are good radiators and if the temperature of the environment is not much lower than the temperature of the blood, while this is traversing the part, heat will be lost to the environment until the venous blood has reached the same temperature as the surroundings. When we then know how much heat has been given out by the part to the water surrounding it in a given time, and we know the difference in temperature of the inflowing and outflowing blood we can easily calculate the blood passed in a unit of time, per unit of mass. The formula used for the calculation is, $Q = \frac{H}{T - T_1}$. H being the calories of heat given up to the calorimeter; T being the temperature of the arterial blood; T_1 being the temperature of the venous blood. We must know the cooling curve and the specific heat of the calorimeter. Stewart worked with a calorimeter especially made for this purpose and found the average blood flow in adults to be 14 c.c. of blood per hundred grams of hand in one minute.

As the results obtained by this method have never been checked up by results obtained by determining the actual blood flow, some experiments on dogs with Tigerstedt's modification of Ludwig's Strohmur

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35. Thomas: Biochem. Ztschr. **57**:456, 1913.
36. Hornemann: Biochem. Ztschr. **57**:473, 1913.
37. Hewlett and Zwaluwenburg: Heart **1**:87, 1909.
38. Stewart: Heart **3**:33, 1911.

have been done in the physiologic laboratory of Washington University under the direction of Dr. Erlanger. The blood flow was determined on five dogs using the iliac artery on the same side as Stewart's method had been applied directly before the operation. The results will be seen from Table 7.

TABLE 7.—Determination of Blood Flow Using Iliac Artery

No.		Weight in Gm.	Stewart Method, Calc. per 100 C.c. Mass in 1 Min.	Strohmur Method, Calc. per 100 C.c. Mass in 1 Min.	Blood Pressure in Mm. Hg
1	Normal dog..........................	6,100	15.4 c.c.	14.4 c.c.	128
2	Normal..............................	5,200	10.0 c.c.	10.4 c.c.	120
3	Starved dog (8 days)...............	4,720	11.16 c.c.	10.67 c.c.	110
4	Starved dog (5 days)...............	2,200	5.12 c.c.	4.30 c.c.	105
5	Starved dog (10 days).............	5,200	7.60 c.c.	4.30 c.c.	90

The figures correspond very well except in one instance.

On applying the method to infants, an ordinary large vacuum food jar was used as a calorimeter. The top was closed by a layer of cork and felt with the necessary openings for the hand, thermometer and stirrer. Since, as far as I know, no studies have ever been made on the blood flow in infancy the rate in normal infants had to be determined first.

TABLE 8.—Blood Flow of Normal Infants

Number	Age	C.c. of Blood per 100 Gm. of Arm (right) per Min.	Number	Age	C.c. of Blood per 100 Gm. of Arm (right) per Min.
1	¼ month	14	16	7½ months	10
2	1 month	15	17	8 months	17
3	2½ months	15	18	9 months	19
4	3 months	19	19	9 months	15
5	2 months	15	20	13 months	16
6	3 months	16	21	13 months	19
7	3 months	18	22	16 months	17
8	3 months	20	23	17 months	14
9	3½ months	20	24	18 months	20
10	4 months	17	25	19 months	14
11	4 months	17	26	20 months	19
12	4 months	21	27	24 months	16
13	4 months	16	28	2½ years	15
14	6 months	20	29	2½ years	15
15	6½ months	22		Average	17.3

It will be seen that the rate of blood flow in the right arm of a normal infant is fairly constant and varies from 14 to 22 c.c. with an average of 17.3 c.c. of blood per hundred c.c. of arm per minute. Determinations made on the foot showed two-thirds of the value for the hand, that is to say, from 11 to 12 c.c. per hundred c.c. of body

If we take 17 c.c. as the normal flow for infants, we find that the blood circulation in infants is higher than in adults, a fact which I had previously suspected (Utheim[39]) without having been able to prove.

In table 9 are given the results obtained on the blood flow of athreptic infants. In the case of a number of these infants, several determinations were made on different days and when the infants were in various states of nutrition. These results are recorded. Results are expressed in terms of c.c. of blood per 100 grams of arm per minute.

TABLE 9.—Blood Flow of Athrepic Infants

No.	Age, Mo.	Mo.	C.c.	C.c.	C.c.	C.c.	C.c.	C.c.	C.c.
1	1	6	5	5	5				
2	1	6	6	4	8	12			
3	1	3	3	6					
4	1	5	7						
5	1	7	7						
6	2	6	8						
7	2	5	6	6	7	8			
8	2	5							
9	2	7	7						
10	2	12	5	5	3	14			
11	3	7							
12	3	5							
13	3	10							
14	3	8							
15	3	9							
16	3	3	2	1	2	4	3	4	0
17	3	8	3	4					
18	4	3	3						
19	4	5	8	15	15	15	15		
20	4	6							
21	4	9							
22	4	5	3	2	3	2	4		
23	5	17	22	14	6	3			
24	5	4							
25	5	2	3	4	3				
26	5	7	5	2					
27	5	13	17	13	18	11	18		
28	5	7	9	3					
29	5	8							
30	6	5	3	3					
31	6	3	6						
32	9	4	3	4	2	4	5	1	3
34	17	11	8						
35	18	8	9						

Comparison between the blood flow of athreptic infants (Table 9) and of infants suffering from various diseases (Table 10) indicate that low blood flow is a special attribute of athreptic infants, and of those suffering from acute diarrhea.

Why do these athreptic infants show this very low rate of blood flow?

The factors which determine the rate of blood flow must be considered. These are four: (1) the condition of the heart; (2) changes in blood viscosity; (3) changes in the total blood volume, and (4) influence of the vasomotor system.

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[39] Utheim: Norsk. Mag. f. Lagevidensk **15**:802, 1917.

As to the heart, electrocardiographic studies made on some of the infants in this series by Dr. McCulloch[40] have shown that deviations from the normal type of curve may occur. Such changes are, however, not constantly observed. The blood pressure, as will be seen later, is not usually low. The pulse rate, however, may be slow. There is, at present, not sufficient experimental evidence upon which to base a definite conclusion as to the rôle of the heart in the causation of the low volume flow of the blood. It is certainly necessary to consider other factors.

TABLE 10.—Blood Flow in Infants Suffering From Various Diseases

No.	Age, Mo.	Disease	C.c.	C.c.	C.c.	C.c.	C.c.	C.c.	C.c.
1	2	Anemia..............	27	36	26	28	29	27	17
2	1	Anemia..............	32						
3	7	Anemia..............	31						
4	12	Malnutrition.........	11						
5	6	Malnutrition.........	10						
6	12	Malnutrition.........	12						
7	6	Malnutrition.........	15						
8	9	Malnutrition.........	15						
9	4	Malnutrition.........	13						
10	8	Tuberculosis.........	9						
11	13	Tuberculosis.........	18	11	11	15			
12	22	Tuberculosis.........	11						
13	5	Tuberculosis.........	11						
14	9	Tuberculosis.........	11	12					
15	12	Tuberculosis.........	12						
16	6	Tuberculosis.........	21						
17	12	Tuberculosis.........	12						
18	21	Tuberculosis.........	23						
19	14	Tuberculosis.........	13						
20	20	Rickets..............	12						
21	24	Congenital syphilis..	15						
22	12	Congenital syphilis..	16						
23	6	Meningitis...........	14	13	27	26	25		
24	12	Meningitis...........	19	14	11	32			
25	14	Meningitis...........	8						
26	24	Nephritis............	19						
27	9	Nephritis............	5	8	13	9			
28	24	Nephritis............	11						
29	12	Nephritis............	10						
30	24	Hypothyroidism.....	3						
31	4	Hypothyroidism.....	20						
32	6	Acute diarrhea.......	8	9	8				
33	9	Acute diarrhea.......	2	5	3	3			
34	7	Acute diarrhea.......	16						
35	7	Acute diarrhea.......	5						
36	8	Acute diarrhea.......	3	5					
37	4	Acute diarrhea.......	10	8	12	10	10	10	
38	1	Acute diarrhea.......	7						
39	2	Acute diarrhea.......	6	3					
40	5	Acute diarrhea.......	7	8					

As far as the blood viscosity is concerned, this is, as is well known, a function of the protein concentration. As the protein is low in these infants the change should be on the low side and should tend to increase instead of diminish the circulation.

Passing to the total blood volume, some of the infants examined in this paper showed a diminished blood volume (Marriott[24]) a fact which very well explains the low rate of blood flow. Other cases of athrepsia, however, did not show diminished volume in proportion to the body weight though they showed the same low rate of blood flow. What is the cause in these cases?

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[40] McCulloch: Am. J. Dis. Child. **20**: (Dec.) 1920 (to be published).

The constriction of the peripheral blood vessels must be an important factor.

That such a constriction actually takes place in these emaciated infants seems to be proved by the differences in venous and capillary blood with the higher cell count and hemoglobin content on the capillary side in all cases of athrepsia except one (Table 11).

TABLE 11.—Difference Between Venous and Capillary Blood in Athrepic Infants

No.	Age	Venous			Capillary		
		Erythrocytes	Leukocytes	Hb., per Cent.	Erythrocytes	Leukocytes	Hb., per Cent.
1	1½ mos.	....	......	98	....	......	133
2	4 mos.	....	......	117	....	......	123
3	2 mos.	....	......	91	....	......	99
4	5 wks.	....	......	71	....	......	71
5	3 mos.	....	......	78	....	......	86
6	3 mos.	....	......	100	....	......	117
7	1 mo.	....	......	100	....	......	120
8	4 mos.	....	......	108	....	......	120
9	3 mos.	3,416,000	8,800	78	4.704.000	15.600	102
10	....	4.312,000	12,400	105	4,880,000	17,600	109
11	4 mos.	4,880,000	8,400	98	5,184,000	9,000	105
12	2 mos.	3.296 000	8.000	96	4,056.000	8 600	102
13	2 mos.	2,160,000	8,000	76	2,360,000	8,600	87
14	3 mos.	3,080,000	8,000	83	3,152,000	......	87
15	4 mos.	2,248.000	8,000	80	2,736.000	14,300	91
16	5 mos.	5,565,000	17,000	85	6,480,000	12,200	90
17	2 mos.	2.992.000	19,200	42	3,072,000	24,000	50
18	2 mos.	2,212,000	18 000	38	2,400,000	20.000	43
19	4 mos.	4.100 000	18 000	90	5,392,000	22,000	95
20	2 mos.	1,944 000	13.200	40	2,552,000	14,000	43

TABLE 12.—Difference Between Venous and Capillary Blood in Normal Infants

No.	Age	Venous			Capillary		
		Erythrocytes	Leukocytes	Hb., per Cent.	Erythrocytes	Leukocytes	Hb., per Cent.
1	2 mos.	3,976,000	9,000	119	3,912,000	8,000	120
2	9 mos.	4,560.000	6,400	109	4,136,000	6.500	105
3	14 years	....	......	125	....	......	125
4	3 mos.	....	......	95	....	......	90
5	2 years	....	......	83	....	......	83
6	12 years	....	......	100	....	......	100
7	2 mos.	....	......	83	....	......	83
8	4 mos.	....	......	112	....	......	113
9	....	....	......	76	....	......	78

Most of the hemoglobin determinations were made by Palmer's method;[41] a few were made with the Sahli hemoglobinometer. The Turk counting chamber was used for the cell counts. All determinations were made with the same blood pipette.

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[41] Palmer: J. Biol. Chem. **33**:119, 1918.

Such a difference was not found in normal infants or infants suffering from various diseases, with the exception of some of the cases of acute diarrhea, one case of tuberculosis, one of nephritis and one of meningitis.

The next question then arises. Why does this peripheral constriction take place? A fact will be referred to which is mentioned later. These infants have to be considered as being in the same physical condition as a starved animal, that is, an organism which has nothing to waste and works in the most economical way. In order to diminish the loss of heat from the body surface a peripheral constriction takes place. The blood, then, naturally is distributed from the peripheral parts of the body to the internal organs.

TABLE 13.—DIFFERENCE BETWEEN VENOUS AND CAPILLARY BLOOD IN DIFFERENT DISEASES

No.	Age	Disease	Venous			Capillary		
			Erythrocytes	Leukocytes	Hb., %	Erythrocytes	Leukocytes	Hb., %
1	8 yrs.	Tuberculosis...........	....	......	111	....	......	107
2	9 yrs.	Heart disease..........	....	......	120	....	......	105
3	9 yrs.	Heart disease..........	....	......	123	....	......	117
4	2 yrs.	Anemia.................	....	......	57	....	......	57
5	12 mos.	Tuberculosis...........	....	......	94	....	......	82
6	15 mos.	Meningitis.............	....	......	78	....	......	78
7	9 mos.	Tuberculosis...........	....	......	80	....	......	87
8	4 mos.	Tuberculosis...........	....	......	91	....	......	91
9	2 mos.	Tuberculosis...........	....	......	85	....	......	86
10	6 mos.	Acute diarrhea.........	....	......	83	....	......	87
11	13½ mos.	Meningitis.............	....	......	81	....	......	107
12	9 mos.	Ileocolitis.............	....	......	87	....	......	87
13	3 yrs.	Acidosis...............	....	......	97	....	......	97
14	1 yr.	Meningitis.............	....	......	114	....	......	114
15	2 yrs.	Nephritis..............	....	......	91	....	......	100
16	6 mos.	Malnutrition...........	....	......	111	....	......	111
17	8 mos.	Acute diarrhea.........	5,134,000	......	81	6,352,000	......	87
18	2 mos.	Acute diarrhea.........	3,536,000	16,400	65	4,064,000	18,400	70

It is easy to understand how this low rate of blood flow, in some instances from 80 to 90 per cent. less than normal, could be a factor which, together with the high water content of the blood, would still further lower the resistance of these infants.

On account of lack of nourishment, the body cells will degenerate, the oxidizing power of the body tissue will diminish and the organism will progressively be broken down.

THE BLOOD PRESSURE IN ATHREPTIC INFANTS

A survey of the literature in regard to blood pressure in infancy reveals rather widely varying values for normal infants. The reasons for this are, as usual, that the methods employed have been different. Examinations have been few and the selection of material has not been sufficiently careful.

TABLE 14.—BLOOD PRESSURE OF NORMAL INFANTS EXPRESSED IN MILLIMETERS OF MERCURY

No.	Age	Systolic	Diastolic	No.	Age	Systolic	Diastolic
1	½ mos.	80	70	17	5 mos.	80	60
2	1 mo.	85	70	18	6 mos.	90	80
3	1½ mos.	90	70	19	8 mos.	85	70
4	2 mos.	85	70	20	9 mos.	85	65
		83	65			85	60
		80	65	21	9 mos.	90	20
5	2 mos.	92	75	22	10 mos.	97	75
6	3 mos.	95	80	23	12 mos.	100	80
		95	75	24	12 mos.	100	80
7	3 mos.	90	75	25	13 mos.	95	75
8	3 mos.	95	85	26	13 mos.	90	60
		95	80	27	14 mos.	98	75
9	3 mos.	95	85	28	15 mos.	95	60
10	4 mos.	95	75	29	16 mos.	100	75
11	4 mos.	90	75	30	16 mos.	105	90
12	4 mos.	95	80	31	19 mos.	105	80
13	4 mos.	95	70	32	20 mos.	98	70
14	4 mos.	95	75	33	24 mos.	100	75
15	4 mos.	95	75	34	24 mos.	100	80
16	5 mos.	85	70	35	28 mos.	95	75
		85	70				

TABLE 15.—BLOOD PRESSURE OF INFANTS SUFFERING FROM VARIOUS DISEASES EXPRESSED IN TERMS OF MILLIMETERS OF MERCURY

No.	Age	Disease	Systolic	Diastolic
1	3 mos.	Tetany	95	90
2	4 mos.	Malnutrition	70	50
			75	50
3	4 mos.	Acute diarrhea	100	95
			99	70
			95	77
4	4 mos.	Adenitis	95	75
5	5 mos.	Miliary tuberculosis	105	95
6	5 mos.	Adenitis	86	65
7	5 mos.	Diarrhea	78	65
8	6 mos.	Pyelitis	100	85
			100	85
9	6 mos.	Acute diarrhea	105	90
10	6 mos.	Malnutrition	65	45
11	7 mos.	Malnutrition	95	75
12	7 mos.	Acute diarrhea	100	80
13	8 mos.	Malnutrition	85	65
			85	65
14	8 mos	Acute diarrhea	88	70
			75	55
15	9 mos.	Tuberculosis	100	80
			105	80
16	9 mos.	Acute diarrhea	100	80
			100	80
17	10 mos.	Pneumonia	94	75
			100	60
18	10 mos.	Otitis media	85	60
19	13 mos.	Epidemic meningitis	105	90
20	13 mos.	Tuberculosis	88	70
			95	80
			95	60
			90	70
			90	70
21	13 mos.	Congenital syphilis	95	75
22	14 mos.	Hypothyroidism	120	80
			120	80
23	14 mos.	Bronchitis	105	70
24	14 mos.	Tuberculosis	105	90
25	15 mos.	Tuberculosis	105	90
			105	90
26	15 mos.	Meningitis	95	80
			95	80
27	15 mos.	Pneumonia	120	60
28	21 mos.	Tuberculosis	90	60
29	24 mos.	Anemia; rickets	105	85
			105	85
30	24 mos.	Tuberculosis	82	55
31	24 mos.	Pneumonia	90	60
32	3 years	Acidosis	115	75

It was found necessary to gather normal material, not in order to make a complete study of the normal blood pressure in infants with its physiologic variations, but in order to be able to compare the results on athreptic infants with results obtained with the same apparatus and in the same way on normal infants. A Tycos sphygmomanometer with a cuff which was made to fit the infant's thigh was used. The auscultatory method was employed. No blood pressures were taken on the arm. The examinations were always made between 7 and 9 p. m. when the infants were most quiet. Only those results obtained from infants who were completely quiet have been recorded.

TABLE 16.—Blood Pressure of Athreptic Infants Expressed in Terms of Millimeters of Mercury

No.	Age, Mo.	Weight, Gm.	Systolic	Diastolic	No.	Age, Mo.	Weight, Gm.	Systolic	Diastolic
1	1	2,625	80	70	15	4	3,500	90	70
			80	70	16	4	2,358	64	35
			80	70				78	60
			85	60				84	55
2	1	2,590	80	70					
3	1	2,500	83	55	17	4	2,860	92	65
4	2	3,625	95	85				85	30
			95	85					
			90	73	18	4	3,000	83	60
			95	80	19	4	3.500	80	60
5	2	3,375	80	65	20	5	3,800	78	65
6	2	2.160	72	50				92	80
7	2	2,430	88	65				92	80
			94	70					
8	2	2,320	75	60	21	6	3,780	90	75
9	2	3,000	90	70				90	65
			80	55				105	95
			83	60					
			85	55	22	6	4,540	90	75
10	3	3,450	93	80	23	7	3,850	82	55
11	3	3,030	98	80	24	7	4,050	95	25
			98	80	25	9	6,075	105	88
12	4	4,225	87	73				105	89
13	4	4,330	100	90				105	85
			95	85				105	85
			95	79				95	70
14	4	2,800	92	75					
			105	85	26	12	6,240	85	70
			100	75	27	17	6,450	85	70
			92	75				90	20

From Tables 14, 15 and 16 it will be seen that the blood pressure of athreptic infants usually does not differ very much from that of normal infants of the same age and from infants suffering from various diseases. In exceptional cases low pressures have been observed (Cases 6, 16, 20). It should be mentioned that the results obtained at the thigh are higher than those of other authors who have used the arm for the determination, evidently due to the fact that the cuff is applied to a larger limb.

PART II. ANIMAL EXPERIMENTS. WHAT CHANGES TAKE PLACE IN TOTAL BLOOD VOLUME DURING DIFFERENT STAGES OF NUTRITION?

Some experiments on animals (rabbits) have been done in order to determine what changes take place in total blood volume during different stages of nutrition and especially to follow the blood volume during a prolonged under feeding period after having brought the weight down to an abnormally low level for the animal, a nutritional condition comparable to athrepsia.

The blood protein, blood flow and hemoglobin were followed during these changes in the nutritional condition in order to see in what relationship these factors stand to the total blood volume of the organism.

For purposes of comparison the blood protein and blood flow in normal animals were first determined (Tables 17 and 18).

TABLE 17.—Blood Protein in Normal Rabbits

No.	Weight, Gm.	Protein, per Cent.	No.	Weight, Gm.	Protein, per Cent.
1	1,700	6.34	16	3,050	6.65
2	1,600	6.34	17	2,850	8.28
3	2,100	6.12	18	2,330	6.98
4	1,700	5.03	19	2,570	6.98
5	1,950	6.98	20	2,050	6.55
6	1,720	5.90	21	1,920	6.55
7	1,600	6.34	22	2,700	6.12
8	1,820	5.68	23	2,750	6.55
9	1,820	6.12	24	2,500	6.22
10	1,750	6.55	25	2,550	6.12
11	900	6.00	26	2,500	6.44
12	1,720	6.12	27	2,700	6.44
13	1,380	6.22	28	2,150	6.55
14	2,430	6.22	29	2,650	6.55
15	3,120	6.22			Aver. 6.40

TABLE 18.—Blood Flow of Normal Rabbits Expressed in Terms of C.c. of Blood Per Hundred C.c. of Mass of Hind Leg in One Minute

No.	Weight, Gm.	Flow, C.c.	No.	Weight, Gm.	Flow, C.c.
12	1,450	10.64	23	2.250	7.00
13	1,520	8.50	24	2,500	7.58
14	2,330	6.44	25	2,700	7.50
15	3,120	12.80	26	2,500	10 90
16	3.050	8.20	27	2,700	9.80
17	2,850	9.50	28	2,140	9.50
18	2,270	10.60	29	2,750	6.16
19	2,560	12.80	30	1,800	5.80
20	1,860	10.75	31	2,150	8.41
21	1,760	14.00	39	2,400	9.00
22	2,700	10.00			Aver. 8.8

The normal blood protein for rabbits weighing from 1,000 to 3,000 gm. averages 6.40 per cent.

Normal rabbits weighing from 1,500 to 3,000 gm. of weight show from 5.8 c.c. to 14 c.c. with an average of 8.8 c.c. of blood flow per hundred c.c. of leg per minute. As far as the total blood volume is concerned, it was of especial importance in this work to use a method which required little loss of blood and does no harm to the animal. Such is the dye method of Keith, Rowntree and Geraghty,[42] the principle of which is the introduction directly into the circulation of a nontoxic, slowly absorbable dye which remains in the plasma long enough for thorough mixing and the determining of its concentration in the plasma calorimetrically by comparison with a suitable standard mixture of the dye and serum. Such a dye is vital red.

Those who have made the most careful studies of blood volume in animals are, perhaps, Dreyer, Ray and Walker,[43] who determined blood volume in rabbits indirectly by bleeding. They found the normal blood volume of a rabbit weighing from 2,000 to 3,000 gm. to be from 4 to 5 per cent. of the body weight.

The results which I have obtained on rabbits appear in Table 19.

TABLE 19.—BLOOD VOLUME OF NORMAL RABBITS

No.	Weight, Gm.	Plasma Vol., C c.	Blood Vol., C.c.	Per Cent. of Body Weight	"K"
3	2,100	65	92.8	5.1	1.76
5	1,800	70	100.0	5.5	1.48
6	1,675	60	85.7	5.1	1.64
7	1,520	56	82.6	5.5	1.60
8	1,800	70	100.0	5.4	1.48
10	1,800	50	71.0	...	1.64
12	1,820	50	83.3	4.5	1.79
14	2,440	73	108.9	4.5	1.79
15	3,130	80	123.0	4.0	1.73
16	3,050	80	129.0	4.2	1.63
17	2,850	75	115.3	4.04	1.74
18	2,330	72	112.5	4.8	1.59
19	2.570	87	133.8	5.1	1.40
20	2,050	64	104.9	5.1	1.57
21	1,550	64	98.4	5.5	1.48
22	2,700	87	124.7	4.6	1.55
23	2,250	70	116.6	5.2	1.48
24	2,500	73	115.8	4.6	1.59
25	2,450	68	106.2	4.2	1.71
26	2.500	80	123.0	4.9	1.50
27	2,700	75	122.8	4.5	1.58
28	2,150	66	104.7	4.8	1.59
29	2,700	77	122.2	4.4	1.59
Average					1.60

When we compare these results on normal rabbits with the results of Dreyer, Ray and Walker we see that they correspond very closely, which shows that the method used in this work is entirely reliable. It is necessary to note however, that if there is either hemolysis or lipemia present in the blood specimens the results cannot be used.

Dreyer, Ray and Walker [43] have called special attention to the fact that blood volume is a function of the surface area of the animal;

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[42] Keith, Rowntree and Geraghty: Arch. Int. Med. **16**:547 (Oct.) 1915.

[43] Dreyer, Ray and Walker: Phil. Tr. Roy. Soc. London **201**:133, 1910, Ser. B.

that is to say, the smaller animals have a relatively larger blood volume than heavier animals of the same species and this fact may be expressed by the formula based on Meeh's [44] formula for determining the surface area of the body from its weight. The formula used in warm-blooded animals is: $B = \frac{W^{2/3}}{K}$, B being blood in c.c.; W being the weight of the animal in grams and K being a constant to be calculated for each species of animal by experimental determination of the total blood volume and substituting this for B in the equation $K = \frac{W^{2/3}}{B}$, he found K for rabbits to be 1.59. According to my experiments $K = 1.60$. His statement is once more confirmed that the relationship between blood volume and surface area of the animal is a fairly constant one.

When we now pass to the changes taking place during different stages of nutrition it should be mentioned that various authors have differed considerably in the results obtained. Panum,[45] Voit [46] and London [47] of the earlier authors feel convinced on the basis of their material that in animals (dogs and rabbits) subjected to complete and exhausting starvation there is no change in the proportion of blood to body weight. On the other hand, Bidder and Smith [48] take an opposite point of view. A. Rasmussen and G. Rasmussen [49] found in a recent study that the blood volume in woodchucks is lowest when the animals contained a maximum of fat. After dormancy and before food is available the percentage of blood is again high and the most emaciated animals have the highest percentage of blood in proportion to body weight.

My rabbit experiments were done in the following way: After a complete examination of blood volume, blood flow, blood protein, hemoglobin and corpuscular volume the animals were completely fasted, neither food nor water being given until the weight was reduced to the lowest point compatible with life. At this stage all the determinations were repeated. An amount of food and water just sufficient to prevent further drop in weight was then given and the determinations repeated at intervals. Most of the rabbits for months practically maintained their weight at a level much below normal. Others gained a little but were again brought down to the low level and remained there until death occurred.

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44. Meeh: Ztschr. f. Biol. **15**:425, 1879.
45. Panum: Virchows Arch. f. path. Anat. **29**:241, 1864.
46. Voit: Ztschr. f. Biol. **30**:510, 1894.
47. London: Arch. f. Biol. Wissensch. **4**:516, 1896; Abstr. from Muhlmann: Centrabl. f. allg. Anat. u. path. Anat. **10**:186, 1899.
48. Bidder and Smith: Die Verdauungssafte und der Stoffwechel, 1852, p. 332.
49. Rasmussen, A., and Rasmussen, G.: Am. J. Physiol. **44**:132, 1917.

TABLE 20.—Results of Experiments on Fasting and Under-Fed Rabbits

Number	Weight, Gm.	Date	Days Starvation	Days Under-Feeding	Protein, per Cent.	Hb., per Cent.	Corpuscle Volume, per Cent.	Blood Flow, C.c.	Plasma, C.c.	Blood Volume, C.c.	Blood Volume in per Cent. of Body Wt.	Calculated Blood Volume, C.c. K = 1.60	Per Cent. Difference Between Actual and Calculated Blood Volume
3	2,100	9/13	0	0	6.12	60	30	...	65	92.8	5.1	100.1	— 7.8
	1,350	9/24	11	0	6.12	60	25	...	55	73.3	5.4	76.3	— 4.0
4	1,520	9/10	0	0	5.03	75	..	10.6					
	1,070	9/18	8	0	7.20	..	..	1.5					
	1,350	9/22	..	4	5.77	..	..	6.6					
	1,200	10/24	..	34	6.27	70	30	...	48	68.5	5.6	70.61	— 3.0
	1,350	11/ 1	..	46	6.55	..	30	...	58	82.8	6.1	76.3	7.8
	1,320	11/25	..	65	6.34	..	24	...	55	72.3	5.5	75.21	— 4.0
7	1,520	9/10	0	0	6.34	65	32	...	56	82.6	5.5	82.62	0
	1,270	9/17	7	0	6.12	70	27	...	52.5	71.5	5.5	73.30	— 2.5
	1,320	10/ 8	..	21	....	..	..	...	49	64.4	4.9	75.21	—16.7
8	1,800	9/13	0	0	5.68	60	30	...	70	100.0	5.4	92.48	7.5
	1,185	9/19	6	0	6.22	55	..	...	50	60.9	5.14	70.0	—14.9
9	1,850	9/14	0	0	6.12	70	35	...	48	73.0	4.02	94.2	—29.0
	1,430	9/24	10	0	....	..	..	...	42	57.0	4.03	79.3	—39.0
	1,200	10/ 6	..	11	7.63	..	30	...	46	65.7	5.4	70.61	— 7.4
	1,310	10/20	..	25	6.77	..	33	...	50	74.6	5.7	74.83	— 0.2
	1,120	11/ 8	..	44	6.22	35	..	...	50	59.5	5.0	67.41	—13.2
10	1,800	9/11	0	0	6.55	75	30	...	50	71.0	...	92.5	—30.2
	1,220	9/20	9	0	7.63	75	20	...	48	60.0	4.8	71.4	—19.0
	1,150	10/ 7	..	17	6.12								
	1,130	10/21	..	32	7.20	52	..	...	52	67.5	6.0	67.80	— 0.4
	1,160	11/ 8	..	49	7.52	54	22	...	51	65.3	5.5	69.00	— 5.6
12	1,820	9/10	0	0	6.12	75	..	...	50	83.3	4.5	93.2	—11.8
	1,150	9/19	9	0	5.25	75	25.5	...	40	55.9	4.8	68.60	—22.7
14	2,440	11/ 1	0	0	6.72	70	33	6.4	73	108.9	4.5	113.3	— 4.0
	1,560	11/18	17	0	7.63	90	36	1.0	55	85.9	5.5	90.10	— 4.9
	1,680	11/28	..	10	6.55	70	27	6.76	70	95.8	5.6	88.32	7.8
	1,775	12/20	..	32	6.22	58	25	...	88	117.3	6.6	91.63	13.3
	1,970	1/ 9	..	52	6.34	60	26	...	93	125.6	6.3	98.2	21.7
15	3,130	10/ 4	0	0	6.32	90	35	12.8	80	123.0	4.0	133.7	— 8.7
	2,160	11/ 8	14	0	8.06	90	39	1.0	60	98.3	4.5	104.4	— 6.2
	2,650	11/28	..	25	5.47	65	30	7.25	88	125.7	4.7	119.7	4.9
	2,550	12/21	..	47	5.90	60	24	...	110	144.7	5.6	116.7	15.0
	2,370	1/ 9	..	66	6.34	62	27	...	109	135.6	5.6	111.1	18.0
16	3.050	11/ 4	0	0	6.65	80	38	8.2	80	129.0	4.2	131.4	— 1.8
	1,980	11/17	14	0	8.0	85	..	2.0	60	93.7	4.7	98.5	— 5.1
	2,520	11/28	..	10	6.12	62	37	9.24	68	107.4	4.2	115.0	— 6.5
	2,250	12/28	..	40	6.55	80	33	...	87	128.3	5.6	108.3	15.6
	2,520	1/11	..	54	6.98	65	33	...	86	128.3	5.1	115.7	9.0
17	2,850	11/ 1	0	0	8.28	75	35	9.5	75	115.3	4.04	125.60	— 8.8
	1,845	11/14	13	0	10.09	110	38	0.8	57	91.9	4.9	95.47	— 3.0
	1,800	11/26	..	12	8.49	80	37	...	85	103.1	5.7	92.48	10.0
18	2,330	11/ 6	0	0	6.98	85	36	10.60	72	112.5	4.8	110.8	1.5
	1,590	11/16	10	0	9.0	85	26	2.2	60	93.7	5.8	85.24	9.0
	1,920	11/29	..	13	6.55	62	23	11.31	80	103.8	5.4	96.56	7.0
	1,980	12/20	..	35	6.34	70	22	...	80	102.5	5.1	98.55	3.9
	1,830	1/10	..	55	6.34	60	26	...	83	112.1	6.1	93.51	16.5
20	2,050	10/30	0	0	6.55	80	39	10.75	64	104.9	5.1	100.9	3.8
	1,230	11/13	14	0	7.20	80	27	3.5	52	71.2	5.7	71.75	0
	1,440	11/26	..	13	7.08	70	32	9.8	67	98.5	6.8	79.70	8.9
	1,380	12/18	..	34	8.06	..	..	...	70	94.5	6.8	77.47	18.0
	1,350	1/ 9	..	56	6.98	58	27	7.8	78	106.8	7.8	76.3	28.5
21	1,750	10/30	0	0	6.55	70	35	14.00	64	98.4	5.5	90.76	7.7
	1,350	11/ 6	6	0	8.06	..	23	1.68	58	75.3	5.5	76.3	— 1.0
22	2,700	10/31	0	0	6.12	70	30	10.0	87	124.7	4.6	121.2	2.8
	1,980	11/16	16	0	6.87	80	35	1.2	70	107.6	5.4	98.55	8.3
	2,130	11/29	..	13	5.68	65	29	6.6	68	95.7	4.4	103.50	— 8.9
	1,620	12/20	..	34	5.68	55	26	...	90	120.0	7.4	86.21	28.1
23	2,250	11/ 6	0	0	6.55	75	40	7.0	70	116.6	5.2	108.3	7.1
	1,560	11/15	9	0	7.42	76	36	1.0	52	81.2	5.2	90.10	—10.9
	1,720	11/29	..	14	6.77	..	31	11.20	70	101.4	5.7	89.72	11.5
	1,520	12/28	..	43	6.98	53	23	...	85	103.9	7.2	82.62	20.5
	1,750	1/12	..	58	6.98	53	27	10.7	83	113.7	6.5	90.77	20.3
24	2,500	11/ 4	0	0	6.22	85	37	7.5	73	115.8	4.6	115.2	0
	1,775	11/18	14	0	7.20	85	35	1.7	62	95.3	5.4	96.12	— 0.1
25	2,450	11/ 4	0	0	6.12	90	36	7.5	68	106.2	4.2	113.6	— 6.5
	1,815	11/18	14	0	8.06	85	31	1.7	52	75.3	4.1	93.0	—23.9
	2,090	11/29	..	11	6.34	70	28	13.33	64	88.8	4.3	103.20	—16.2
	1,875	12/18	..	30	7.63	..	33	...	71	105.9	5.6	94.9	10.3

TABLE 20.—RESULTS OF EXPERIMENTS ON FASTING AND UNDER-FED RABBITS—(*Continued*)

Number	Weight, Gm.	Date	Days Starvation	Days Under-Feeding	Protein, per Cent.	Hb., per Cent.	Corpuscle Volume, per Cent.	Blood Flow, C.c.	Plasma, C.c.	Blood Volume, C.c.	Blood Volume in per Cent. of Body Wt.	Calculated Blood Volume, C.c. K = 1.60	Per Cent. Difference Between Actual and Calcium Blood Volume
	2,020	1/ 9	..	52	7.20	70	34	8.0	70	106.0	5.2	99.87	5.6
26	2,500	11/ 1	0	0	6.44	70	35	10.9	80	123.0	4.9	115.10	6.4
	1,620	11/15	14	0	7.63	..	30	0.8	65	92.8	5.7	86.21	7.1
	1,890	11/26	..	11	6.00	..	25	11.89	66	88.0	4.1	95.54	— 8.5
	1,830	12/21	..	35	....	60	27	...	75	102.7	5.6	93.51	8.9
	1,730	1/10	..	55	6.34	65	33	...	72	107.4	6.1	90.05	15.7
27	2,700	11/ 1	0	0	6.44	70	39	9.8	75	122.8	4.5	121.2	1.3
	1,800	11/18	17	0	8.28	80	35	1.5	63	96.5	5.3	92.5	4.1
	1,970	11/28	..	10	6.98	63	27	3.16	71	98.6	5.0	98.22	0.4
	1,800	12/18	..	30	7.63	..	24	...	78.5	103.2	5.2	92.48	10.3
	1,900	12/29	..	41	6.34	55	23	8.32					
	2,220	1/10	..	53	7.20	65	27	...	92	126.0	5.7	106.30	8.1
28	2,150	11/ 2	0	0	6.55	75	37	9.5	66	104.7	4.8	106.5	— 1.7
	1,320	11/16	14	0	6.77	75	37	1.3	40	63.4	4.8	75.21	—18.6

In referring to Table 20 it will be seen that twenty-one rabbits were examined in the way described. Of these six died at the end of complete starvation and fifteen were followed in the period of prolonged underfeeding. According to the formula $B = \frac{W^{2/3}}{K}$, K being calculated from my own measurements on normal rabbits, a theoretical blood volume has been determined and the present difference between the actual and theoretical blood volume put in one column.

It will be seen that most of the rabbits in the second determination, that is, the day after the longest complete starvation before food and water had been given, showed a negative difference between the actual and theoretical blood volume, that is, they have at this stage a smaller volume than they should have according to the surface area. The differences are, however, sometimes very small.

That it is mostly water which disappears from the blood in this period of complete starvation can be seen from the amounts of protein, hemoglobin and corpuscular volume which rise during this period.

The blood flow decreases from the normal 8 or 10 c.c. to as low as 1 c.c. after the longest periods of starvation. This is, of course, due partly to the diminished volume, but, as mentioned before, since the difference between the actual and theoretical value is very little we must think of other factors. The blood flow determined in these experiments is the peripheral flow, the rate through the rabbit's hind legs. We know from experience that nature is always the most economical worker. With lack of food the animals keep quiet, by contraction of the peripheral arterioles heat may be conserved and the blood distributed to those organs whose functional activity is essential to life. In this way the low rate of blood flow found is explained.

As soon as fluid and food were given those rabbits, even when no more than enough to prevent further loss of weight, the blood volume in most cases was rapidly restored. The protein concentration became normal and blood flow increased. Figure 4 (rabbit 14) shows graphically the changes here mentioned.

Four of the rabbits did not reach a positive difference between actual and calculated blood volume during under-feeding (Nos. 4, 7, 9 and 10, Table 20). Of these, however, two (Nos. 9 and 10) showed a negative difference in the first control observations, and one (No. 7) showed no difference whatever, and on one (No. 4) the normal result was not taken. It is of interest to note that all these four rabbits failed to gain in weight even though plenty of food was given, and two of them (Nos. 9 and 10) developed skin infections. The skin infection did not affect any of the others, though all were kept in the same room. It is, perhaps, only fair to attribute the poor condition of these four rabbits at least in part to the low blood volume.

SUMMARY

It is found in this study that the serum protein in normal infants is from 6 to 6.5 per cent. and remains at this level until the tenth or eleventh month, when the protein begins to rise, and by the fifteenth month it has reached the same level as found in adults, that is, about 8 per cent.

Infants suffering from various diseases show, with the exception of exudative diathesis and nephritis, no remarkable change in blood protein concentration, while infants with acute diarrhea or vomiting have a high per cent. of protein, the result of blood concentration.

Premature infants and athreptic infants show a low protein percentage in blood, in many cases as low as 4 per cent. This condition in premature infants is an expression of the influences of age and development on the water metabolism of the organism (Bezold). As far as the athreptic infants are concerned, the low protein in some cases seems to be due to lack of power on the part of the organism to build up protein, in other instances to the over-feeding with carbohydrates.

The high water content of the organism in both premature and athreptic infants must be regarded as an important factor in the low immunity they show, thus predisposing these infants to multiple infections.

Besides this high water content of the organism, the athreptic infants show a very low rate of blood flow which in some instances is due partly to the diminished blood volume, in other instances to constriction of the peripheral small vessels in order to accomplish the distribution of the blood to the internal organs. This constriction of the peripheral vessels is proved by the differences found in the blood count and hemoglobin content between capillary and venous blood. The low blood flow is not usually accompanied by a lowering of blood pressure because of the following compensatory factors: (1) a diminution of the blood bed by atrophy of the skin, subcutaneous tissue and musculature; (2) the contraction of the small peripheral vessels; (3) possible changes in the alimentary blood vessels (Schiff).

This low rate of blood flow will contribute in lessening the resistance of these infants by depriving the body tissue of the necessary food and in this way contributes to the breakdown of the body cells.

Experiments on rabbits have shown that during complete starvation with deprivation of fluid, the blood volume falls below the normal value for the body surface as a result of water loss from the blood. However, by giving only enough food and water to prevent further weight loss the blood volume is rapidly restored and quickly reaches a value above normal for the body surface. Four rabbits did not completely regain the normal volume. These were rabbits which did badly and would not gain even if food was given in abundant amount. It is only fair to place the poor condition of these four animals in relation to the low blood volume. When we apply these findings to infants we can see that in athreptic infants who show a lowering of blood volume all the above mentioned factors will still further affect the organism and all factors will work together in lowering the oxidizing power of the body cells and favor a breaking down of body tissues.

I wish to express my sincere thanks to Dr. W. McKim Marriott who suggested and directed this study.

AMYOTONIA CONGENITA *

N. O. PEARCE, M.D.

MINNEAPOLIS

The condition known as amyotonia congenita, first described by Oppenheim in 1900 [1] is frequently referred to as Oppenheim's disease. In 1903, Batten [2] described the same condition without reference to Oppenheim's work, under the name of infantile type of myopathy. Kundt,[3] Collier and Wilson,[4] Rothman,[5] Chene,[6] Griffith,[7] Cassirer [8] and Thorspeken [9] have all made valuable contribution to the literature in this subject. Marburg,[10] Kaumheimer [11] and Foot [12] have made exhaustive studies of the histologic changes in the muscles and in the nervous systems. Until recently about 136 cases have been reported in the literature, but in many of these the diagnosis has been questioned by other contributors. Of this number thirty cases were reported by Americans, twenty-six by Italians, thirty-three by Germans, twenty-one by Englishmen, seventeen by Frenchmen, three by Belgians, two by the Dutch, one case by a Swiss, and one case by a Russian. The best recent reviews with reports of cases are those of Reuben [13] and Faber [14] who have attempted a statistical analysis of the case reports.

The condition is generally defined as a disease beginning at or before birth or in early infancy, probably due to a congenital developmental defect of the lower motor neurons and of the voluntary muscles. Clinically it is characterized by weakness, hypertonia and quantitatively diminished electrical response in the muscles, usually without disturbance of sensation or mentality.

Of the five cases reported in this paper, the first (W. H.) is of interest largely because of the classical symptomatology and the

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1. Oppenheim, H.: Monatschr. f. Psychiat. u. Neurol. **8**:232, 1900.
2. Batten, F. E.: Brain **26**:147, 1903.
3. Kundt, W.: Inaug. Diss., Leipzig, 1905.
4. Collier and Wilson: Brain **31**:1, 1908.
5. Rothmann, M.: Monatschr. f. Psychiat. u. Neurol. **25**:161, 1909.
6. Chene: Thése de Paris, 1910.
7. Griffith, J. C.: Tr. Am. Ped. Soc. **22**:184, 1910; Am. J. M. Sc. **142**:165, 1911.
8. Cassirer, R.: Handb. d. Neurol. Lewandowsky **2**:230, 1911.
9. Thorspeken, O.: Jahrb. f. Kinderh. **76**:300, 1912.
10. Marburg, O.: Arb. a. d. neurol. Inst. a. d. Wien. Univ. **19**:133, 1911.
11. Kaumheimer, L.: Jahrb. f. Kinderh. **78**:170, 1913.
12. Foot, N. C.: Am. J. Dis. Child. **5**:359 (March) 1913.
13. Rueben, M. S.: Arch. Int. Med. **20**:657 (Nov.) 1917.
14. Faber, H. K.: Am. J. Dis. Child. **13**:305 (Sept.) 1917.

results of the exhaustive metabolism study carried out.[15] The second and third cases (R. W. and K. W.), and the fourth and fifth cases (R. L. and B. L.) are believed to be the first authentic instances reported of twins suffering from the disease. Literature reveals only one other instance in which twins have been mentioned, a case reported by Reiner,[16] in which one twin died intrapartum.

REPORT OF CASES

Case 1.—W. H., a boy, was aged 3½ years. Nationality, American.

Family History.—The mother was 38 years of age, and of a very nervous disposition. As a child she continuously dropped things from her hands and has always been unable to write or do needlework if nervous or excited because of a tremor of the hands. She has been subject to severe recurrent headaches for years. She was 34 years of age when the patient was born, and had been married eight years, this being her first conception. While pregnant she was very nervous, suffered considerably from sleeplessness, and complained of intense itching over the body. The first movements were felt at four months, and were very vigorous from that time on. Labor was prolonged and difficult, and the child was evidently asphyxiated, being described as a "blue baby." A second child was born, eighteen months after the patient. The mother was in slightly better health while carrying this baby. She believes that he was more active when first born than the older child. He seemed to be well until the third or fourth week, at which time he became constipated and could retain no food, developed convulsions in a few days and died. The mother is not certain as to the cause of death.

The father of these children was 38 years of age. He had suffered considerably from rheumatism, and had some heart trouble. His family history was negative, except that his mother died of a convulsion. The Wassermann reaction was negative in father, mother and patient.

Personal History.—The child was born at full term after a prolonged and difficult labor, in an asphyxiated condition. The birth weight was eight pounds. He was nursed on the breast with complementary feedings until 5 months of age, at which time he was put entirely on artificial food. The mother stated that the baby never nursed well, and never seemed to be hungry or at all interested in his food, although he gained in weight. She noticed a fine tremor of both hands which, as she remembered, was present from birth. He never kicked like other babies and was never able to roll over or change his position in any way. He began to talk when 9 months old, and at 3½ years was exceptionally bright mentally. He spoke somewhat slowly with a slight quaver in his voice as though there was difficulty in articulation. At 9 months he was able to sit up if helped and supported, but at no time had he been able to raise himself voluntarily. When sitting up, if his head fell backward he was unable to raise it again. He was inclined to be nervous, cried easily and for long periods. He was, when last seen, on a general diet, but showed a decided lack of interest in his meals, going without food for forty-eight hours apparently without the slightest discomfort.

Physical Examination.—The patient appeared to be overnourished, but was flabby with a general lack of muscular tone seeming to involve all of the voluntary muscles of the body. His color was good. He was very bright and interested in his surroundings. His head was well shaped, with a circumference of 50 cm. The fontanel is closed. The teeth and tonsils were in excellent condition. The pupils reacted normally, there seemed to be no weakness or paralysis of the facial muscles and no enlargement of the glands. There was a marked deformity of the chest, which was 54 cm. in circumference. The sternum was thrust forward and upward, with lateral recessions of the ribs and marked kyphosis posteriorly, which was more accentuated when sitting up. Both physical and roentgen-ray examinations showed nothing abnormal in the heart or lungs, although breathing was of purely abdominal type. No vasomotor disturbances were apparent. The abdomen was rather prominent. There was a marked tendency to constipation. Neither the liver nor the spleen were palpable. The limbs are symmetrical and there are no contractures or deformities. All superficial and deep reflexes were absent. The sense of pain and reactions to heat and cold were acute. The pad feet described in this disease were very noticeable. A fine tremor of both hands appears on the slightest exertion, but there were no spasms, twitchings, choreiform movements, or convulsions. The patient was able to perform the natural movements with both arms and legs within narrow limits, but only in a weak and uncertain manner. There was excessive mobility of the joints. The skin was normal in appearance and there was no edema present, but it was impossible to wrinkle up the skin apart from the underlying tissues. The von Pirquet reaction was negative, and the roentgen-ray examination showed nothing abnormal in the bony structure.

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[15] Pearce, N. O., and Ziegler, M. R.: J. Biol. Chem., 1920.

[16] Reiner, H.: Berl. klin. Wchnschr. **50**:1306, 1913.

Laboratory Findings.—The routine hospital urine examination showed nothing abnormal: Hemoglobin, 94 per cent.; leukocytes, 10,600; erythrocytes, 4,800,000. Differential count: Polymorphonuclears, 41 per cent.; lymphocytes, 53 per cent.; large mononuclears, 1 per cent.; transitionals, 2 per cent.; eosinophils, 3 per cent. There was no response to electrical stimulus under 5 milliamperes. There was great difficulty in obtaining specimens of blood for chemical examination. The usual skin punctures, even when done repeatedly, produced only minimum amounts of bleeding.

Microscopic Findings.—A small piece of muscle was obtained and sections were cut in paraffin. Only a few fibers of normal size were found in the sections. These occurred for the most part in a single group, but a few were scattered throughout the section. Nearly all the fibers were greatly reduced in size, the diameter being usually about one-tenth that of the normal. Many muscle fasciculi contained only atrophic fibers. The fibers showed no abnormality, except a decrease in size and in indistinctness of the fibrillae. There was no hyalin degeneration or necrosis. The relative size and the arrangement of the atrophic fibers may be seen in Figures 1, 2 and 3, each of which contain one or more normal fibers.

Treatment.—The patient also had cod liver oil and phosphorus over long periods, and a thorough tryout of thyroid and mixed gland therapy was given without any definite improvement. Under careful diet with rather large amounts of protein, with oil rubs and expert massage and carefully executed regular exercise, and with the support of a light body brace, the patient showed some slight improvement in muscular status. He suffered an acute attack of pneumonia in March, 1919, but made a normal recovery with no marked change in his general condition.

Cases 2 and 3.—R. W. and K. W. were twin boys, 22 months old.

Two older children were both living and well at the time of this examination. The mother was 26 years of age, the father 31. The family history of both parents was negative, and they both appeared to be sturdy, well developed and in excellent health. One of the older children did not walk until 2½ years of age, but, according to the mother, seemed to be quite normal at this time. The history of the pregnancy presented nothing unusual, the mother having felt movements at about the usual time and of the usual strength. K. W., the first born, was a breech delivery at full term and was breast fed for sixteen months. The mother had noticed nothing wrong with him, except for the weakness of his legs and inability to stand.

Physical Examination.—K. W. was fairly well developed and well nourished, and of good color. The head was well shaped and the fontanel not quite closed. The eyes were normal, with no nystagmus or strabismus. The hearing was good, and the teeth and throat were in excellent condition. The chest was well shaped, heart and lungs were normal, and breathing was normal in type. The abdomen was normal in size and shape, with the liver palpable at the costal margin, and spleen not palpable. The extremities were symmetrical, the musculature of the arms and hands being well developed and with normal function. There was a decided lack of muscular tone in the lower extremities, the movements being weak and uncertain. There was no vasomotor disturbance. The knee jerks were present, equal but weak and hard to obtain. All other reflexes were present and seemingly normal. There were no contractures, but there was a tendency toward pad feet. There was an abnormal mobility of the joints in the lower extremities. No congenital defects were present. All sphincter controls were normal. The sense of pain was very acute. The electrical reactions showed a kathodal contraction with 4 milliamperes, this being the only case under 5. The mental examination showed an intelligence coefficient of 100 per cent.

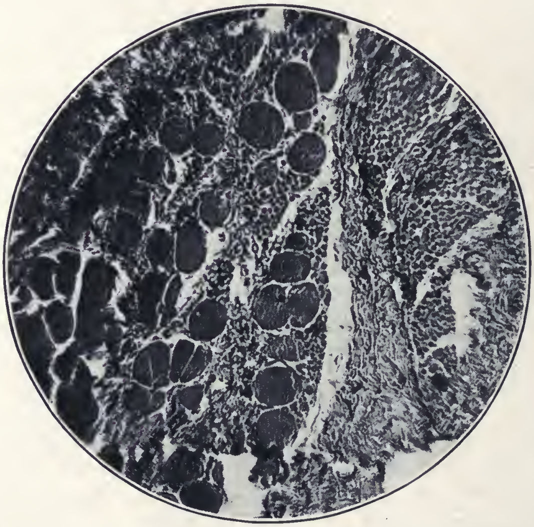

Fig. 1.—A group of normal fibers with a number of atrophic fibers in the same fasciculus. Fasciculus of atrophic fibers on right.

Laboratory Examination.—The Wassermann and von Pirquet reactions were both negative. The routine hospital urine examination was negative. Blood: Hemoglobin, 75 per cent.; leukocytes, 13,600; erythrocytes, 4,120,000. Differential count: Polymorphonuclears, 26 per cent.; large lymphocytes, 5 per cent.; small lymphocytes, 57 per cent.; eosinophils, 12 per cent. The basal metabolism was not quite successful because of the child's crying, but was probably normal.

Case 3.—R. W., full term twin of K. W., had a normal birth, weighing six pounds. He was too weak to nurse, however. At 3 months of age he developed some febrile condition, and at 14 months he contracted pneumonia, from which he recovered very slowly. At the time of examination he was 22 months of age, had never been able to sit alone, and found great difficulty in changing his position. When placed on his back, he could not turn over. He talked quite well, but the voice was weak, both when speaking and crying.

Physical Examination.—The patient was very poorly developed and nourished, and his color was poor. There was extreme flabbiness and lack of muscular tone throughout the body and extremities. A weakness of the facial muscles, with a lack of normal expression, was very noticeable. When propped up, he could not hold his head erect. The head was well shaped, and the fontanel almost closed. Vision was good; eye and pupil reflexes were normal; hearing was good, and teeth and throat were in good condition. The cervical lymph nodes were somewhat enlarged. There was extreme deformity of the chest with abdominal type of breathing. The sternum was pushed forward and upward, with marked recession of the ribs on both sides. There was a kyphosis, with lateral curvature of the spine which was much more pronounced when the child was propped up in a sitting position. The heart sounds were normal. There were a few diffuse coarse râles in both the right and left lungs. The abdomen was large and flabby, but there was no constipation. The liver was palpable 5 cm. below the costal margin; the spleen was not palpable. All tendon reflexes, as well as the abdominal and cremasteric reflexes, were absent. The sensation to heat, cold and pain was normal.. The patient could grasp objects feebly with the hands, and with great effort he could raise the hand to the mouth. He could move his legs about, but very feebly. An abnormal mobility of the joints was very marked. There were no contractures or congenital deformities; no tremors or choreiform movements. The pad feet were very typical. Sphincter control was normal. The mental examination showed a normal intelligence, although the patient was somewhat handicapped in responding to tests because of the inability to use his hands.

Laboratory Examination.—The Wassermann and von Pirquet reactions were negative, also the urine examination. Blood: Hemoglobin, 65 per cent.; leukocytes, 7,800. Differential count: Polymorphonuclears, 30 per cent.; large lymphocytes, 5 per cent.; small lymphocytes, 65 per cent. With electrical reaction no response was obtained under 10 milliamperes. There was a definitely lowered basal metabolism. The skin phenomenon noted in Case 1 was also prominent in this case.

Cases 4 and 5.—R. L. and B. L., twin boy and girl, were 7 months of age at the time of the examination.

The father was 32 years of age. He had some heart trouble, but was able to work. He seemed to be robust, active and in good health, but had been weak as an infant. He was one of a large family, of which all members are in good health. The mother was 32 years of age, was rather a nervous type of woman, but well developed and seemingly in good health. She had been married ten years. She had a miscarriage during the first year, but two years later gave birth to a full term normal child, who was at this time 7 years of age. Since that time there had been no conception until that of the present patients. During this pregnancy the mother had very severe and persistent headaches, and was much swollen about the hips and abdomen. Vomiting was very persistent and she was entirely incapacitated a good deal of the time. Movements were felt at four and one-half months, and were very strong during the latter part of the pregnancy.

R. L., baby girl, twin of B. L., 7 months of age, was the first born, with low forceps delivery, and was in good condition. Birth weight was 7 pounds; the weight at examination was 14½ pounds. The baby was never very active and did not try to change her position. She had always nursed feebly, and has seemed weaker since an attack of pneumonia at 4 months.

Physical Examination.—The child was fairly well developed and nourished, but her flesh was flabby and pallor was rather pronounced. The head was well shaped, normal in size, with slight cranial tabes, and the fontanel normally open. The eye and pupil reflexes were normal, vision seemed good, and no nystagmus or strabismus was apparent. The hearing seemed to be normal. The expression was rather set and the cry feeble. The lack of desire for food was very pronounced, and the mother stated that neither of the twins had ever shown the slightest interest in food, and that it had been only with the greatest difficulty that she had been able to get them to take the required nourishment. Both had always been constipated. This baby at 7 months had no teeth. The throat was in good condition, the chest well shaped, but breathing was purely abdominal in type. The heart and lung sounds were good; the abdomen was soft and flabby, with the liver palpable 2 cm. below the costal margin. The spleen was enlarged and palpable. There was a general weakness of all extremities with contractures of the adductors of the thighs and of the supernators of the forearms. The patient was unable to move her legs, the only motion she was capable of making being that of the toes. There was abnormal mobility of the joints of the ankles, knees and shoulders. The arms were moved about in a rather weak, uncertain manner, and the patient grasped objects only feebly. There were no tremors or twitchings. Both deep and superficial reflexes were absent throughout. Sphincter control was good. There was a moderate degree of pad feet, and the same general skin condition as noted in Case 1. The response to heat or cold was normal, and there was prompt response to pain.

Laboratory Examination.—The routine hospital urine and blood examination disclosed nothing abnormal. The Wassermann and von Pirquet reactions were negative. There was no response to electrical stimulus under 5 milliamperes and no vasomotor disturbance was found.

B. L., the 7 months old baby boy, twin of R. L., was the second to be born. The child was delivered in breech position and was somewhat asphyxiated. The birth weight was 5 pounds, and at the time of examination he weighed 12 pounds. He had had only breast feedings. An attack of pneumonia at 4 months left him weaker than he had been previously. The mother noticed directly after birth that the infant was not strong, and she had great difficulty in giving him sufficient nourishment, as he would take nothing but the breast and seemed too weak to nurse an adequate amount. The patient was pale, somewhat atrophic, rachitic in type, with marked craniotabes and a large fontanel. There was a masklike expression of the face, and the cry was very weak. The eye reflexes were normal, with no nystagmus or strabismus. Sight and hearing were apparently normal. There were no teeth, and the tongue had a tendency to fall back in the mouth. The chest was badly deformed, with the sternum shoved forward and upward, with lateral recession of the ribs. The heart and lung sounds were good, but breathing was purely of the abdominal type. The abdomen was rather prominent and flabby and the child was chronically constipated. The spleen was enlarged and the liver palpable 2 cm. below the costal margin. The patient was totally incapable of moving the legs, the only movement possible being a slight wiggling of the toes. The arms were moved about feebly and uncertainly, and the ability to grasp objects was even less than in Case 4. The child was unable to support the head alone. There was abnormal mobility of the joints, as described in Case 4, and the same contractures were present but to a lesser degree. The pad feet were very marked. The deep and superficial reflexes were all absent, but the response to pain, heat or cold appeared normal. Sphincter control was good and the intelligence normal. There was no response to electrical stimulus under 5 milliamperes. No vasomotor disturbance was found.

Laboratory Examination.—The routine hospital urinary and blood findings were normal. The Wassermann and von Pirquet reactions were negative.

In summarizing the conditions in these five cases, an attempt is made to compare the symptoms and findings with the statistical analysis as published in the papers of Faber and Reuben.

Etiology.—In all five cases the symptoms were present to a more or less degree since birth, a fact noted in the large majority of the cases previously reported. The Wassermann reaction was negative in each case, the previous records showing only fourteen cases in which the Wassermann test had been made, twelve reactions being negative and two positive. The von Pirquet reaction was negative in all five cases, it having been previously reported in but nine cases, all of which were negative.

The question of heredity has been raised by Faber who pointed out familial occurrence in three instances. It will be noted that in the cases of R. W. and K. W. an older brother did not walk until 2½ years of age, and in the case of W. H., a younger child died in early infancy from some unexplained condition, while the history of extreme nervousness and tremor of the hands in the mother is also suggestive.

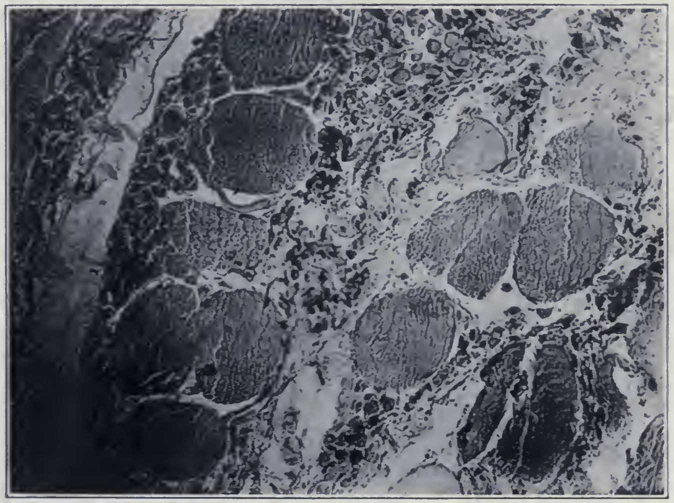

Fig. 2.—High power photomicrograph of Figure 1, showing atrophic and normal fibers in the same fasciculus.

Relative to the analogy between this condition and mongolism as representative of reproductive exhaustion, it will be seen that in the case of W. H. the mother was 34 years of age and this was her first conception after eight years of married life. In the cases of R. L and B. L. almost seven years had elapsed since the birth of an older child. Quickening has been reported absent in six cases, weak in twelve, and retarded in two, but this is not in accord with our cases, as quickening took place at the normal time in all three pregnancies and the movements were especially vigorous in two and normal in the third. The lack of movements has been given as a reason to believe the disease congenital, but that this is not necessarily the case is demonstrated by the fact that the prenatal movements were either normal or unusually vigorous in these cases, although the disease was marked at birth in the case of at least three of the infants. All of our children were full term babies, which seems to be usual, but three of them were asphyxiated at birth, which may or may not have some bearing on the degree of involvement. As regards sex, in the cases reported there was about an even division, while in cases of this report four were male and one female.

Symptoms.—In Faber's analysis, the lower extremities were involved in all cases. which was also true in our patients, the upper extremities in 93 per cent. of his and four out of the five we report. Thoracic respiratory muscles have been mentioned as involved in twenty-six cases and normal in three, while in our patients four were involved and one was normal. The muscles of the trunk were affected in seventy-three instances and normal in seven; in ours we found involvement in all but one. The disease was found to affect the neck muscles in sixty-five of Faber's cases. They were not involved in eleven cases. In four of our cases they were affected. Facial muscles of deglutition and articulation were reported as involved in five cases only, but in ours we felt that there was some involvement in four of the five cases under consideration. The sphincters have always been normal in all cases.

The knee-jerks were absent in sixty-nine cases, diminished in seventeen, present in five and normal in two, while in our cases they were absent in three, very weak in one, and sluggish in one, the same condition prevailing in the other tendon reflexes. The abdominal reflex was present in one of our cases and absent in four, while in the cases reported, where notes have been made the reflex has been noted as absent in about 50 per cent.

Contractures have been present in only two of our five cases, in both upper and lower limbs, while in previous case reports we find thirty-five cases of contractures, twenty-nine of the lower and six of the upper extremities. Abnormality of the joints is almost a constant feature.

The pad feet were described as typical of the disease by Collier and Wilson[4] but are rarely mentioned by other authors, although they were markedly noticeable in three of our patients. Other congenital defects have been noted in about twenty of the cases reported; however, many of these, such as hernias, dislocation of the hips, shoulders and thumbs, and malposition of the feet, might very well be secondary to the general weakness of the supporting muscle rather than a primary developmental defect.

The enlarged spleen noted in Cases 4 and 5 was not mentioned in the other reports.

Vasomotor disturbance has been noted in a few cases but was not found in ours. The deformity of the chest which was prominent in three out of five of our cases, has been seen in fifteen of those previously reported. No characteristic bony change which would not be secondary to weakened musculature has been found in any instance. Speech was slightly affected in two of our cases and the cry was noted as weak in all, which seems to be of common occurrence. Sensation as represented by the reaction to heat and cold and pain was normal in all of our patients as well as in the others reported.

Differential Diagnosis.—In preparing these cases for report, a study of the literature disclosed a considerable confusion in the differentiation of Oppenheim's disease from the different types of muscular dystrophies and progressive muscular atrophies occurring in young children. This is largely brought about because of this lack of detail in the records of case reports, and the various authors who have tried to make statistical analysis, and bring about proper classification, have had to base their conclusions on very incomplete and inadequate data. Further study with more detailed and better case reports will undoubtedly result in a much simpler classification. The condition which we find most difficult to differentiate clearly from Oppenheim's disease is that type of infantile myopathy described by Werdnig-Hoffman in 1891. The clinical symptomatology set forth as being diagnostic of these two types of infantile muscular disease, when

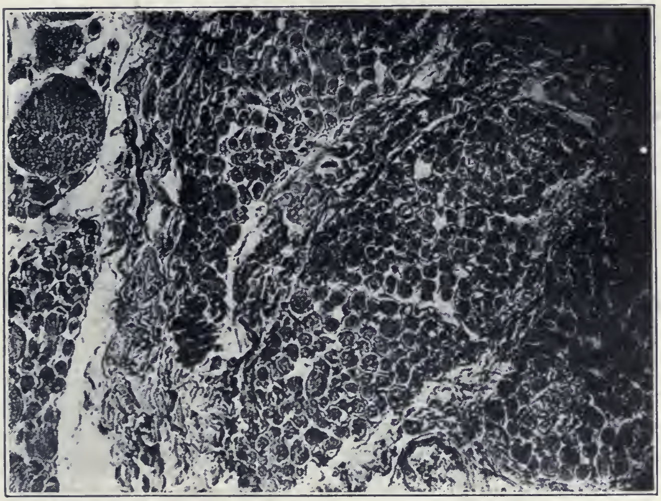

Fig. 3.—Fasciculus of atrophic fibers under moderately high magnification. One normal fiber.

applied to my cases, leaves no sharp line of distinction or differentiation. The Werdnig-Hoffman type is described as being hereditary and familial, but that Oppenheim's type is also sometimes familial is well brought out by the family histories in Cases 2 and 3. It is thought that the Werdnig-Hoffman type is not present at birth and that its onset is gradual and occurs during the second six months. The history of such onset may easily be attributed to lack of observation on the part of those in attendance as is very often the case in Oppenheim's disease, as demonstrated in Case 3 where the mother believed nothing was wrong with the child until it was brought in for examination when 22 months of age. But careful questioning brought out the fact that the weakness had been present from birth. The location of the muscular involvement depends on the severity of the disease and does not present any marked point for differentiation. The involvement of shoulders, back and thighs, supposed to be typical of the Werdnig-Hoffman type, was present in four of the cases here reported. Atrophy, presented as a point of differentiation, was present to a slight degree in Case 5, while the twin, Case 4, was apparently well nourished. The tendon reflexes in Oppenheim's disease vary with the degree of involvement. Twitching and tremors are stated to be present occasionally in the Werdnig-Hoffman type but are not observed in Oppenheim's type. It will be remembered, however, that in Case 1, clinically presenting a classical picture of Oppenheim's disease, a fine tremor of both hands was present. The Werdnig-Hoffman type is supposed to grow progressively worse, while in the Oppenheim type improvement is to be expected. In our report, one patient, Case 3, is becoming progressively worse, while the twin, Case 2, is improving. In cases 4 and 5, involvement is nearly complete, with a tendency to become progressively worse. In Case 1 a slight improvement may be noted. One must conclude, as suggested by Huenekens, that clinically there is no sharp line of differentiation between the Werdnig-Hoffman and the Oppenheim types of this infantile muscular disease.

METABOLISM STUDIES IN CASE 1, W. H.

CHEMICAL WORK DONE BY MILDRED R. ZIEGLER

Although amyotonia congenita has been the subject of a considerable amount of research from the clinical viewpoint, little has been done along chemical lines. A careful review of the literature on the subject reveals only three references concerning the chemistry of Oppenheim's disease. Spriggs[17] published this first chemical research, making a study of the creatinin and uric acid excretion. By comparing the results obtained by him from an experiment with a boy suffering from Oppenheim's disease with a normal boy of the same age and practically the same weight, he showed that creatinin excretion is diminished to less than half the normal amount, while the uric acid excretion remains normal. Sprigg' statement concerning this creatinin was confirmed in 1912 by Gittings and Pemberton [18] who also established a normal calcium retention. The case studied by Powis and Raper [19] which was associated with some nutritional disturbance and acholia, was decidedly different from those cases previously mentioned.

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[17] Spriggs, E. I.: Quart. J. M. **1**:63, 1907.

Chemical evidence, in addition to the statements regarding creatinin metabolism, leads one to believe that amyotonia congenita is a disease caused by protein decomposition. The studies above mentioned covered very short periods, seven, five and four days respectively. We hoped by a longer period to obtain an accurate statement of metabolism with special reference to nitrogen and sulphur urinary partitions since both, if not normal, would be indicative, if present, of protein decomposition.

Case 1, because of the classical symptomatology, was selected for this exhaustive research. During the experimental period, which lasted for a month, the patient was kept on a creatinin-free diet. This period, which commenced and ended with a starvation period, was followed by a dose of charcoal. The excellent method of McCrudden for performing metabolism experiments was rigidly adhered to throughout by a special nurse. The food, feces and urine were collected for twenty-four hour periods, and the urine was analyzed daily, except in two or three instances when two-day specimens were mixed and a daily average was taken. The feces were combined in periods of three and four days, analyzed and the average taken. The food analyses were made in the same way. The volume of urine was about one-half the normal amount for a child of this age, due probably to the fact that the child was largely on a vegetable diet. To avoid increase or variation in the nitrogenous elimination by flushing the tissues, the fluid intake was kept as high and as near constant as possible.

The urine was always acid, and contained no protein or sugar. The indican test was negative and acetone was rarely present. The only thing of interest in the urinary sediment was the presence of calcium phosphate crystals.

The child weighed 13.49 kg. at the beginning of the experiment, and at the end it weighed 13.21 kg. The average daily intake was 53.5 calories per kilogram of body weight which is about 25 calories less per kilogram than for a normal child of this age.

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[18] Gittings, J. C., and Pemberton, M. S.: Am. J. M. Sc. **144**:732, 1912.

[19] Powis, F., and Raper, H. S.: Quart. J. M. **10**:7, 1917.

The complete data with tables and discussion of the results of this experiment will appear in another article [15] and therefore only a summary of the findings are included here.

SUMMARY

Blood analyses made at the commencement of this experiment show the following results:

Creatinin, 1.50 mg. per hundred c.c. of blood.
Creatin, 5.45 mg. per hundred c.c. of blood.
Calcium, 7.10 mg. per hundred c.c. of blood.
Urea nitrogen, 3.50 mg. per hundred c.c. of blood.
Blood sugar, 14 per cent.

The low urea figure may be of some significance. The significant facts, most of which suggest protein decomposition, as demonstrated by a chemical study of this case are:

1. A lowered creatinin excretion, in addition to the excretion of creatin on a low protein diet.

2. A normal uric acid excretion, therefore no nucleo-proteins broken down.

3. An increased rest nitrogen accompanied by an increased neutral sulphur.

4. A normal phosphorus excretion, therefore no bone disintegration.

AMYOTONIA CONGENITA (OPPENHEIM)

REPORT OF A CASE WITH FULL HISTOPATHOLOGIC EXAMINATION *

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Carefully studied cases of amyotonia congenita still deserve the attention of clinicians. Though notable advances in our knowledge of the disease have been made during the twenty years that have elapsed since Oppenheim first described the clinical picture of the condition (1900), there yet remains much that is obscure. Approximately 125 cases of the disease have been reported and are generally accepted as examples of amyotonia congenita. These published cases have recently been analyzed statistically by Faber,[1] who is led to define the condition as "a disease beginning at birth or in early infancy due to a congenital developmental defect of the lower motor neuron and of the voluntary muscles, clinically characterized by weakness, hypotonia and a quantitatively diminished electrical response in the muscles, usually without disturbance of a sensation or of mentality." Spiller,[2] on the other hand, viewing the disease chiefly from the clinical side, has directed destructive criticism against acceptance of the condition as a clinical entity at all. The work of Batten,[3] Kundt,[4] Collier and Wilson,[5] Rothmann,[6] Thorspecken [7] and others has shown that the disease does not always occur in the classical form; many

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[1] Faber, Harold K.: Amyotonia Congenita: A Survey of the Known Cases with a Report of Three New Cases, Am. J. Dis. Child. **13**:305 (March) 1917. Cf. Reuben, M. S.: Amyotonia Congenita of Oppenheim, Report of Six Cases with a Full Review of the Literature, Arch. Int. Med. **20**:657 (Nov.) 1917.

[2] Spiller, W. G.: General or Localized Hypotonia of the Muscles in Childhood (Myotonia Congenita), Univ. Penn. Med. Bull. **17**:342, 1905. Ibid.: The Relation of the Myopathies, Brain **36**:75, 1913. Griffith and Spiller: Amyotonia Congenita; A Clinical and Pathological Study, Am. J. M. Sc. **142**:165, 1911.

[3] Batten, F. E.: Three Cases of Myopathy, Infantile Type, Brain **26**:147, 1903; Ibid., Simple Atrophic Case of Myopathy; So-Called "Myotonia Congenita" or "Amyotonia Congenita," Proc. Roy. Soc. Med. **4**: Part 1, Sect. Study Dis. Child., p. 100, 1911.

[4] Kundt, W.: Ueber Myotonia congenita (Oppenheim), Inaug. Diss., Leipzig, 1905.

[5] Collier, J., and Wilson, S. A. K.: Amyotonia Congenita, Brain **31**:1, 1908.

[6] Rothmann, M.: Ueber die anatomische Grundlage der Myatonia congenita, Monatschr. f. Psychiat. u. Neurol. **25**:161, 1909.

[7] Thorspecken, O.: Beitrag zur Kenntniss der Myotonia congenita (Oppenheim), Jahrb. f. Kinderh. **76**:300, 1912.

atypical cases have been described and the resemblance of some of these either to the spinal atrophies (Werdnig-Hoffmann type) or to the muscular dystrophies (myopathies) is marked. Spiller points out that there is no feature, or group of features, that belongs distinctively to amyotonia congenita; each one is shared in common either with the neural atrophies or with the dystrophies, or with both. It is shown that the recorded cases of amyotonia congenita may be arranged in a series which merges imperceptibly into the other forms of dystrophy, and that clinically there is no sharp line of demarcation between them. Nevertheless, Spiller closes his analysis by stating that, after all, "amyotonia has distinguishing features observed in by far the greater number of cases and that cases with exceptions do little more than show that there may be a transition from amyotonia to myopathy without proving that the two diseases are identical, any more than transitional cases between myelopathy and myopathy prove identity of disease."

On the histopathologic side the difficulties are yet greater. Portions of the affected muscles have been excised and studied microscopically (Bing, Collier and Holmes, Skoog and others); and eighteen or more necropsies have been reported. In ten of these, the examinations have been more or less adequate, notably in the cases reported by Marburg,[8] Spiller,[2] Archangelsky and Abrikosoff,[9] Rothmann,[6] Foot,[10] Kaumheimer [11] and Councilman and Dunn.[12]

Oppenheim thought the affection consisted essentially in a retarded development of the muscles; he did not exclude the possibility of an involvement of the nerves or of the anterior horn cells. To Spiller it seemed "that the symptom-complex of amyotonia may depend on purely muscular lesions (Spiller, Lereboullet and Baudoin, Councilman and Dunn), or these muscular lesions may be associated with alteration of the cells of the anterior horns, which in some instances seems to be slight (Lereboullet and Baudoin, Archangelsky and Abrikosoff), in others intense, and when this cellular alteration is intense, the distinction from the Werdnig-Hoffmann of atrophy may be difficult." Kaumheimer (Heidelberg) concluded, as did Rothmann and Foot before him, that the pathologic picture is one of an active

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8. Marburg, O.: Zur Klinik und Pathologie der Myotonia congenita (Oppenheim), Arb. a. d. Neurol. Institut an der Wien. Universitat **19**:133, 1911.

9. Archangelsky, W., and Abrikosoff, A.: Ein Fall von Myatonia congenita (Oppenheim) mit Autopsie, Arch. f. Kinderh. **56**:101, 1911.

10. Foot, N. C.: Report of a Case of Amyotonia Congenita (Myatonia Congenita—Oppenheim), with Necropsy, Am. J. Dis. Child. **5**:359 (Sept.) 1913.

11. Kaumheimer, L.: Zur Pathologie und Klinik der Myatonia congenita (Oppenheim), Jahrb. f. Kinderh. **78**:170, 1913.

12. Councilman, W. T., and Dunn, C. H.: Myotonia Congenita; Report of Case with Autopsy, Am. J. Dis. Child. **2**:340 (Sept.) 1911.

degenerative process attacking a normally developing central nervous system. This process he conceived of as beginning commonly in intra-uterine life and extending in some cases at least well into extra-uterine life. Theories as to the cause of the degeneration he regarded as being as yet matters of pure speculation.

Opposed to this view of an active degenerative process is the view that the disturbance is, in the earlier stages at least, a purely developmental one, a form of abiotrophy. A third view would be that the same influence retards or perverts the development of one or more elements of the neuromuscular apparatus.

In an incrasing number of carefully studied cases of amyotonia congenita the significant lesion seems to lie in the cells of the anterior horns, in the large motor ganglion cells, and that, most distinctively, in those regions where these cells normally reach their greatest development, i. e., in the cervical and lumbar regions. The lesions are to be variously explained according to the views already enumerated. Similar influences may be conceived of as affecting the muscle cells.

The problem is a complex one, and its solution would seem to lie in the accumulation of carefully studied cases.

The findings in a case of amyotonia congenita that appeared in the service of Dr. John Howland are presented herewith. Clinically, the case may be considered a typical one; histopathologically, it is noteworthy in presenting a picture of arrested or retarded development without accompanying signs of degeneration. The microscopic picture of the muscles closely resembles that described by Finkelnburg[13] (Bonn) in a case of myopathy in an infant (cf. Finkelnburg drawings, loc. cit.).

REPORT OF CASE

History.—T. M., a female infant, aged 6 weeks, was admitted to the Harriet Lane Home Feb. 20, 1913, with the complaint "pining away" (Fig. 1).

Family History.—The parents were American born. There was no history of tuberculosis or of syphilis in the family; no miscarriages, no stillbirths. The patient was the third living child. The oldest, aged 12 years, had suffered from "nervous disability" since 1½ years of age; another, aged 9 years, was well. Three children had died; the first of pneumonia following measles, at 13 months of age, another of diphtheria, at 3 years of age, and a third of spinal meningitis, at 5 months (the meningitis followed a fall). No further family history was obtained.

While carrying the patient the mother had felt strong fetal movements at four and one-half months and up to the time of the child's birth. The patient was born in the Johns Hopkins Hospital Obstetrical Service at full term after a labor lasting seven hours and twenty minutes, breech presentation, easy extraction as follows: "Fingers were hooked into both groins and ready extraction of body to shoulder blades effected. Arms easily brought out and head presented slightly more difficulty, but was delivered by Mauriceau method—extraction taking less than two minutes. Child very slightly asphyxiated and responded to mild stimulation. Mother and child in excellent condition. Length of child 52 cm.; weight, 8½ pounds.

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[13] Finkelnburg: Anatomischer Befund bei progresiver Muskeldystrophie in den ersten Lebensjahren, Deutsch. Ztschr. f. Nervenh. **35**:453, 1908.

Previous History.—The child had been breast fed, and nursed from one-half to three quarters of an hour every two hours. The mother described the child as "nursing and nursing and nursing and not getting enough." The child slept poorly, often waking up and whining.

A few days after birth an impairment of movement in the legs was observed by the attending physician; he noted that the condition improved after a few days. The mother stated that the child had always moved its hands a little, except the left arm; and that this difficulty was observed at, or a few days after, birth. The child cried when it was born: it had a weak cry at first.

The child began to get weaker after reaching the age of 1 month. Two weeks later it was admitted to the hospital.

Present Illness.—Physical Examination: On admission, the patient was described as an emaciated infant of rather poor development—weight, 6 pounds 10 ounces. Length, 55 cm.; circumference of head, 35.6 cm.; circumference of chest, 29.4 cm. The anterior and posterior fontanels were open, the sutures not yet ossified. The eyes were apparently normal; the pupils reacted to light. The movements of the face and mouth were symmetrical; the reflex from the lips was present. The movements of the tongue were apparently normal; as was also the appearance of the throat. The voice was weak. The mucous membranes were pale. There was no general glandular enlargement.

The child lay with its head in almost any position; the head was wobbly, but there was a suggestion of a certain amount of stiffness in the deep muscles of the neck.

The breathing was entirely of the abdominal type. On inspiration there was marked retraction of the chest wall over the left side below the level of the third rib. The breath sounds were less well heard over this area. The heart sounds were strong and clear, the apical impulse was visible inside the nipple line; there were no murmurs. The abdomen was prominent; otherwise apparently normal. The skin seemed much too large for the body. In most places the muscles could be felt under the skin. The calf muscles could not be felt. When the child was lifted up with the hands in the axilla, there was definite resistance of the pectorals and the latissimus dorsi muscles. The right arm was held flexed at the elbow; there was definite wrist drop; the biceps was in active contracture; there was flaccidity of the triceps and the extensors of the hand; no movements of extension of the wrist were seen. The left arm was flexed at the elbow, and held to the side; there was some contracture of the pectorals and latissimus dorsi as well of the biceps. The left hand was held slightly flexed and was not particularly loose at the wrist. The hands were long and slender.

The child lay with the legs rotated outward, slightly flexed at the hips, and flexed at the knees and ankles. There was definite contracture of the abductor muscles, and some apparent shortening of the hamstrings; the knees could be brought to a straight line. The child made few but some movements of the legs; there was slight movement of the calf muscles. The ankles were extremely mobile; the feet were long and slightly ape-like, and could be brought to rest against the lower leg.

The knee jerks were not obtained; it was impossible to obtain the reflexes from the contracted bicep muscles. The lip reflex was present; the child took food well. No involvement of the sphincters was noted. Roentgen-ray examination of the skeleton was negative.

Application of the faradic current to the extensor muscles and the ulnar nerve of the left arm, and to the internal and external popliteal nerves of both legs, elicited no response (though the current was sufficiently strong to cause

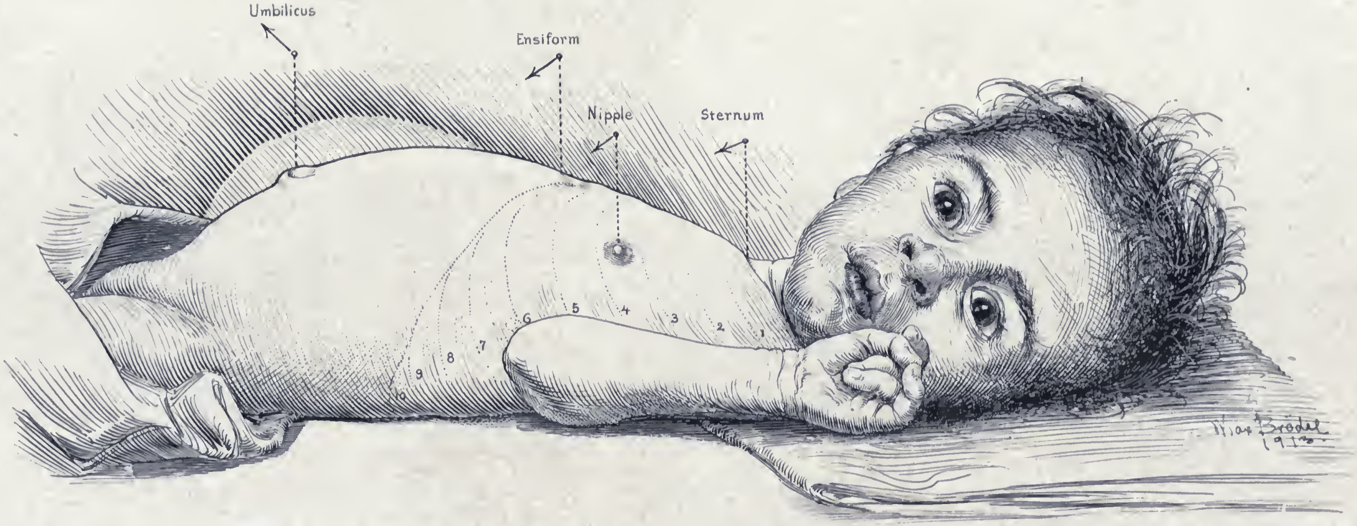

Fig. 1 (Drawing by Mr. Max Brödel).—Shows changes in contour occurring in patient's body during expiration (black) and inspiration (blue). Note especially the depression, or dragging downward of the chest wall during inspiration, due to weakness of the intercostal muscles. The diaphragmatic action being apparently unimpaired, forces the upper abdominal organs downward with resulting protrusion of the abdominal wall.

tetanic contractions in the observer's hand). Application of the galvanic current (cathode, 8 milliampères) to the radial nerve of the left arm and to the popliteal nerves gave no response.

Direct application of the cathode to the extensor muscles of both forearms (very strong current) gave small contractions, and to the extensor muscles of the right arm (from 5 to 6 milliampères) gave very slight contraction; to the right calf muscles (10 milliampères) feeble contraction. These were not the slow, sluggish contractions of the typical reaction of degeneration.

Stimulation of the nerves of the arms and legs with the galvanic and faradic currents gave no response, while galvanic stimulation of the muscles of the forearm and of the muscles of the legs—it was particularly the calf muscles that were stimulated—gave very slight contractions to currents up to 10 milliampères.

The child remained in the hospital eighty-three days, reaching thus the age of 18 weeks.

Treatment.—Surgical: A myringotomy was done during the first week and several times thereafter, with escape of bloody or serous fluid. Excepting slight elevations of temperature that preceded the myringotomies, the patient's temperature was, as a rule, normal until near the close of the period of observation, though there were occasional slight elevations due apparently to superficial skin infection. There was occasional slight leukocytosis.

Dietetic: She received formulas of whole milk and barley water with lactose, and malt soup, and gained in weight steadily, reaching 7 pounds and 10 ounces on the eighty-third day. The stools were of normal appearance; an enema was rarely needed. The urine was negative throughout. Massage was given for nearly a month and then discontinued.

Results: It was noted that the contractures increased from day to day; the arms became equally and more completely flexed at the elbows. The voluntary movements in the arms were eventually reduced to slight movements of the fingers, and those of the legs to slight flexion and extension of the foot and toes.

In a later examination, on the twentieth day of observation, it was noted that the forehead was in constant folds and that the child held the eyes widely open showing sclera about the iris, but that it could close the eyes completely. The eyeballs were very unsteady, constantly moving in almost any direction with a peculiar quick, sharp, snappy jerk. The movement of the eyeballs was not impaired. The pupils reacted to light. The ophthalmoscopic examination was but partially successful, owing to the movements of the child; what was seen of the retina appeared to be normal. The child swallowed readily when the head was turned to the left; with difficulty when turned to the right.

The expression of the child was at this time anxious; she made attempts to cry, as shown by the contraction of the facial muscles, but very rarely was a sound emitted. This was apparently due to insufficient expiratory power on the part of the abdominal muscles.

The type of respiration was noteworthy (Fig. 1). The musculature was thin. The thorax was long and distorted; it was never elevated. With each inspiration it was dragged down toward the vertebral column, as well as toward the umbilicus; with each expiration it rose again, but only to a moderate extent, and the front of the chest as a result of this was much flattened. The movements of the diaphragm were very marked, and caused a great protrusion of the abdomen with each inspiratory effort. This was, perhaps, the result of an unusual attachment of the diaphragm; the fifth rib on the left side was drawn partly behind the sixth in each inspiratory movement. (Inspiratory and expiratory positions are well shown in Figure 1).

Terminal Stage: During the last ten days signs of bronchopneumonia appeared. The child's temperature fell to normal on the eighty-first day of her stay in the hospital; then rose rapidly till it reached 107.6 F. on the morning of the eighty-third day, when the pulse failed and the respiration soon ceased

Comment: Clinically, this case corresponds very closely to cases of amyotonia congenita as described by Oppenheim in 1900. The appearance of the body during respiration, though striking, is entirely in accord with Oppenheim's observation that in severe cases the paralysis involves the intercostals and other muscles of the trunk, but leaves the diaphragm undisturbed. (The unusual attachment of the diaphragm is an anomaly of only passing interest.) In being flattened from before backward, the contour of the thorax in this case differs from that described in Kaumheimer's case ("poorly developed, narrow, pear-shaped, and grooved laterally"), and the somewhat similar findings in Councilman and Dunn's case. The occurrence of contractures is not altogether uncommon in cases of amyotonia congenita, especially in those of longer standing, and has been noted by Collier and Holmes, Collier and Wilson, Haberman (two cases), Ashby, Marburg, Batten, Kundt, Variot and Deviller, and Kraumheimer, among others.[14] It is in the histopathologic findings that the case differs from others that have been described.

Necropsy Findings.—A complete postmortem examination was made six hours after the child's death. The viscera were removed and the body was injected with 10 per cent. liquor formaldehyd solution. The brain and the spinal cord, together with portions of the peripheral nerves and muscles, were then removed and placed in 10 per cent. liquor formaldehyd solution for further study.

Macroscopic: The gross pathologic findings may be summarized as follows: An emaciated infant, muscles everywhere pale and of a reddish gray color, except the diaphragm, which is dark red. The diaphragm is the only normal appearing muscle. Omental fat absent. Practically no epicardial fat present. Myocardium everywhere uniform, but rather pale. Pyloric valve shows nothing unusual, nor does the tongue. Thyroid gland appears normal. The suprarenals are preserved for physiologic examination. Portions of tissue are removed from the biceps, pectoral, intercostal and sartorius muscles, also from the musculocutaneous nerve, which apparently supplied the biceps, and from the sciatic nerve just below the great trochanter, and from the diaphragm.

Microscopic: The general microscopic notes may be summarized as follows: The thyroid and thymus appear normal. The pancreas is thought to show slight hyperplasia of the islands. There is some fragmentation of the heart muscle. Many of the fibers show areas of degeneration where muscle has become rather hyaline and its structure is lost. These areas are fairly frequent, but are small and involve only about 5 per cent. of the muscle fibers. Leukocytes are seen in these areas; they are sometimes seen in the fibers themselves. There is no apparent increase in the interstitial tissue. The general microscopic findings are otherwise unimportant.

Central Nervous System: The membranes covering the brain appear to be quite normal. The brain is of normal size for the age. Stripped of its membranes it weighs 580 gm. (normal weight at from 3 to 6 months, female, 560 gm. (Boyd and Schaefer): 602 gm. (Holt). The general shape of the brain is normal. The fissures are rather more distinct than usual and the convolutions are prominent. This is shown in Figures 2, 3, 4 and 5.

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[14] Strauch, A.: Pathology of Myotonia Congenita, Am. J. Dis. Child. **10:** 16 (July) 1915.

Sections of the cortex were removed from the frontal, motor and calcarine areas as shown in the accompanying photographs, and were subjected to microscopic examination. They show nothing unusual (thionin, toluidin blue and cresyl-violet stains). The normal cells are present. The Betz cells appear normal.

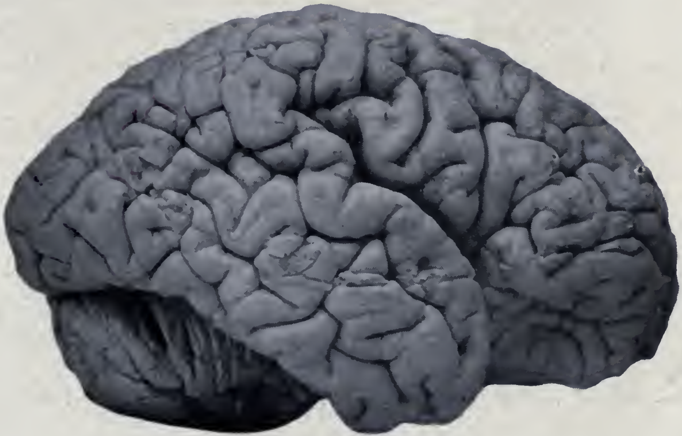


Fig. 2.—Right lateral view of the brain. Normal configuration.

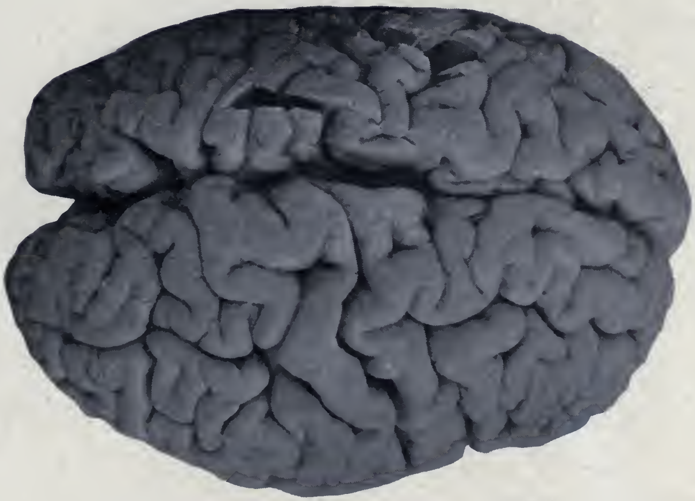


Fig. 3.—Superior surface of the brain. Normal configuration; also sites from which sections had been removed for study.

Spinal Cord: The cord has been slightly injured, during removal, at the sixth dorsal segment; elsewhere it appears to be uninjured. Some spinal ganglia have been lost. On inspection, the membranes present nothing unusual. There is no evidence of any congenital abnormality nor of any inflammatory condition. The blood supply appears to have been normal.

For purposes of comparison, cords and brains were obtained at the postmortem table from stillborn infants, and from premature and full-term infants that had died of acute conditions at ages ranging from 6 hours (subdural hemorrhage) to 14 months. Certain of these were selected for comparison. They may be designated as Cords A, B, C and D, and were obtained from full-term infants dying aged 12, 13, 20 and 28 weeks, respectively.

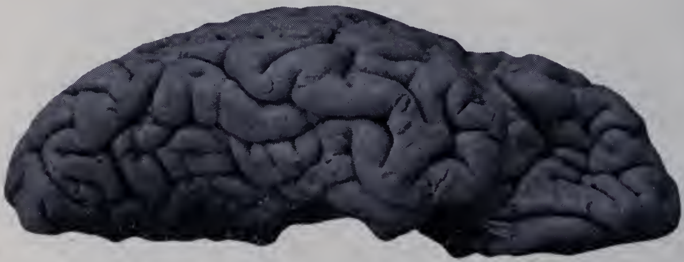


Fig. 4.—Inferior surface of right cerebral hemisphere. Normal configuration.

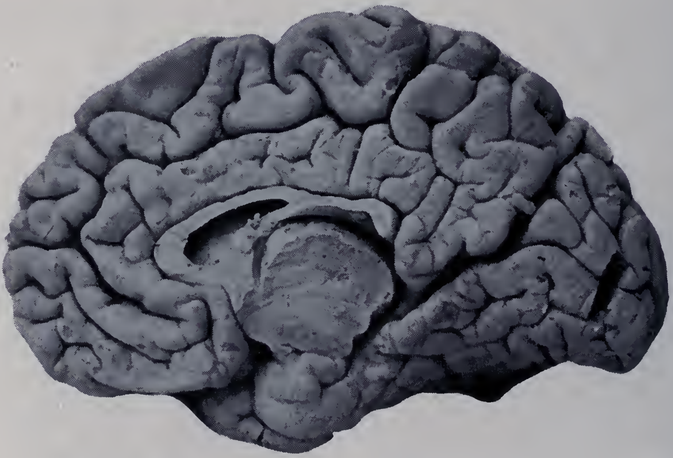


Fig. 5.—Mesial surface of right cerebral hemisphere. Normal configuration, and also site from which sections had been removed for study.

Comparison of our cord (18 weeks) with cords of other infants shows that it is almost as large as Cord D (28 weeks' old child), considerably larger than Cord C (20 weeks) and much larger than Cords A and B (12 and 13 weeks). In form and general appearance the cord most closely resembles Cord D. The dorsal (posterior) roots are little, if any, smaller than the corresponding roots of Cord D, and a little larger than those of Cord C. The ventral (anterior) roots are very much smaller than those of Cord D, and also slightly smaller than those of Cord C. The relation between the size of the anterior roots and posterior roots of our case is 1:3 and 1:4, whereas normally it is 1:2. The fibers of the cauda equina are in size equal to those of Cord D, and larger than those of Cord C.

No appreciable difference in the contour of cross sections from the same levels in the three cords is noted, though there is relative difference in area, as indicated above. There is no evidence of flattening or loss of substance, in the regions of the ventral anterior cornua.

MICROSCOPIC EXAMINATION OF CORD

Microscopic examination of sections from various levels of the cord yields the following results (Figs. 6 to 16, inclusive):

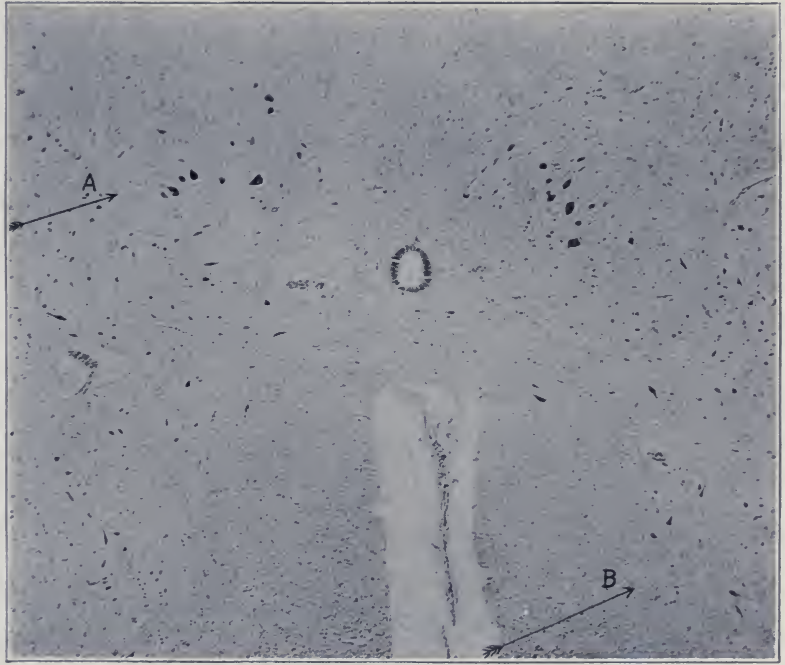


Fig. 6.—Seventh thoracic segment, showing well preserved cells of Clarke's column (A) and almost complete absence of large cells in the ventral (motor) horns (B). No demonstrable gliosis.

There is no evidence of any acute or chronic inflammatory process. No accumulation of polymorphonuclear leukocytes or of small round cells are seen. There is no evidence of recent degeneration—absence of fat and other products of myelin degeneration, as shown by scharlach R and sudan III preparations. Myelinization appears to be normal for a cord of this age (eighteen weeks), as shown by Weigert preparations from C.I and VI, Th.VIII and L.II (Spielmeyer Pal-Weigert technic).

The cells of Clarke's columns are, as a rule, well preserved (Th.VII and L.II). The cells are of normal size as compared with those from cords of infants of about the same age. Certain cells show lateral displacement of the nucleus, but no other abnormal changes are seen.

The large (motor) cells of the anterior horns (C.IV, Th.VIII and L.II) are strikingly few in number (thionin stain), and are, in part, represented by cells that are much smaller in size, but otherwise of the same appearance. These cells, instead of being at least equal in size to those of Clarke's columns, are usually from one fifth to one third or one half the size of these. Only occasionally is a cell of normal size found. Such cells as are found present, as a rule, have a perfectly normal appearance, except that they are small. A few cells show

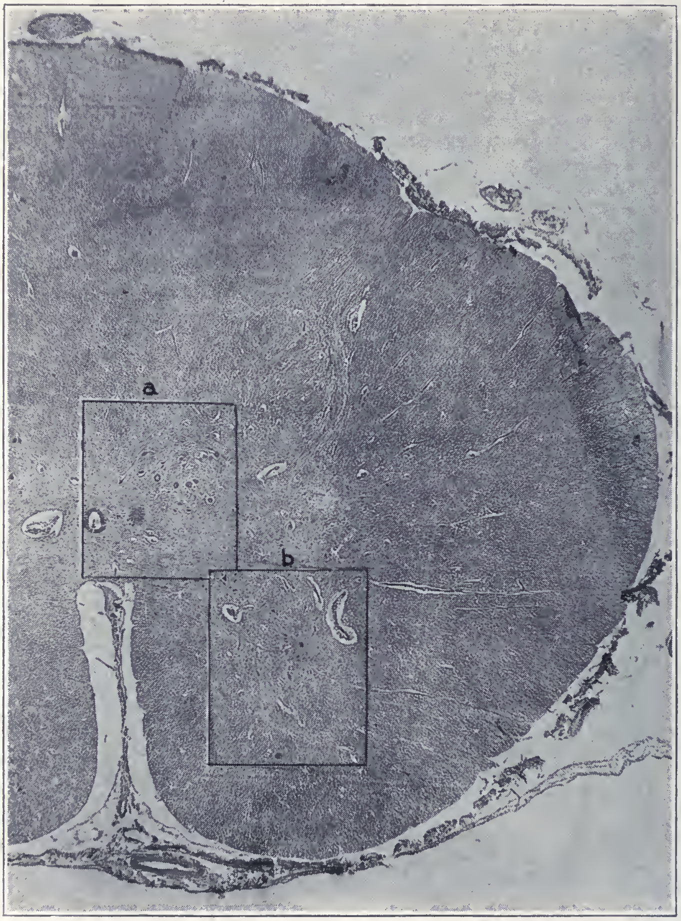


Fig. 7.—Seventh thoracic segment, × 30. Another section showing presence of usual cells in Clarke's column, and almost complete absence of large cells in the ventral (motor) horn. Areas (a) and (b) are shown enlarged in Figures 8 and 9, respectively.

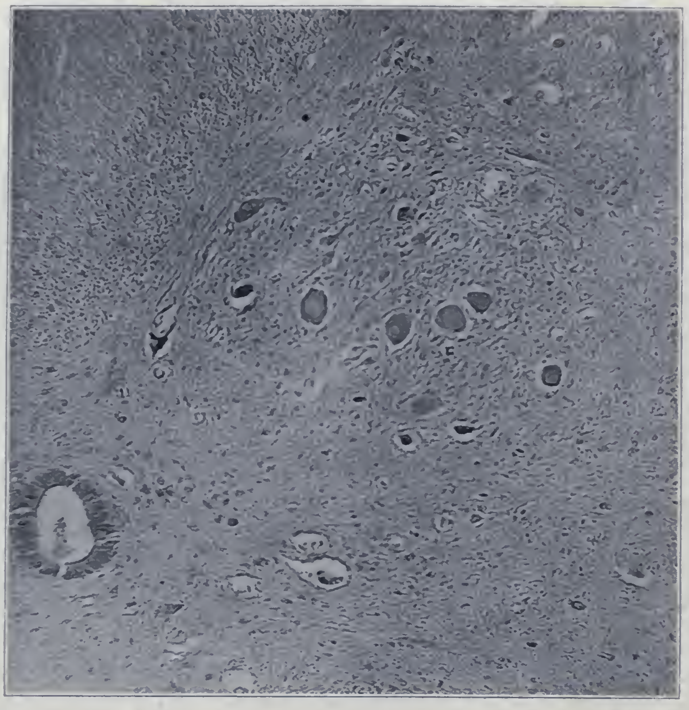


Fig. 8 (× 125).—An enlargement of area a (Clarke's column) in Figure 7.

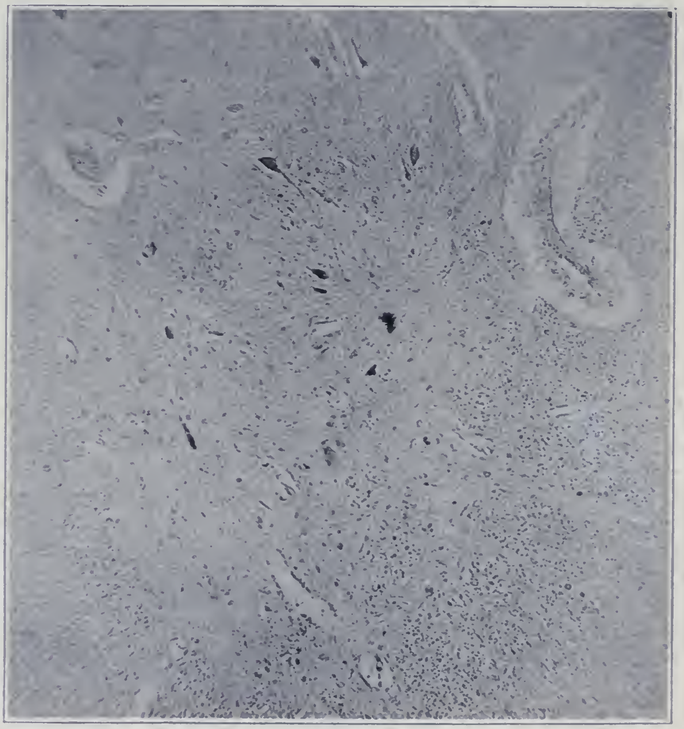
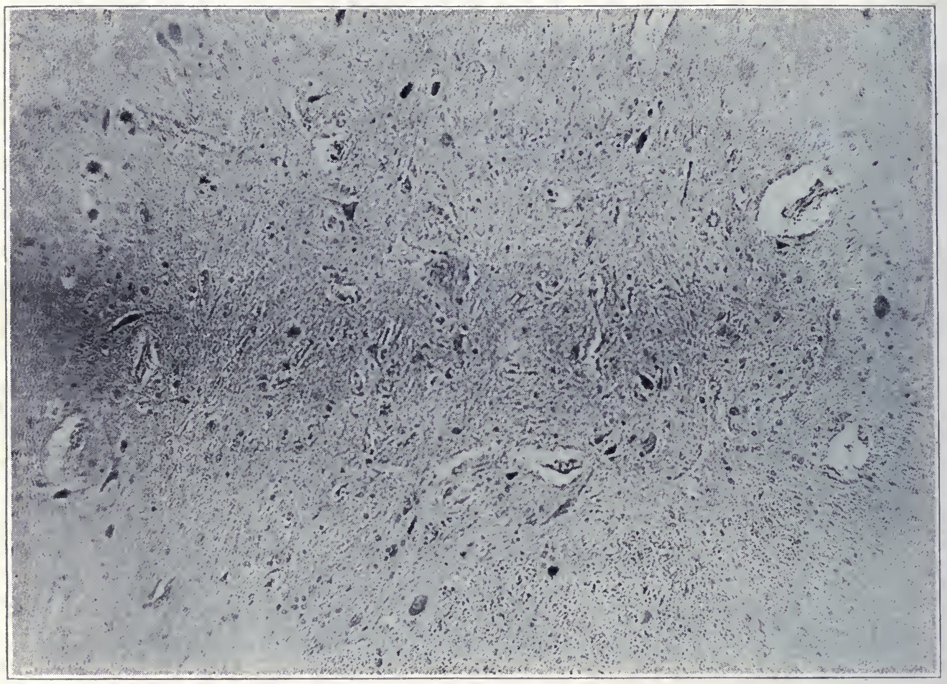
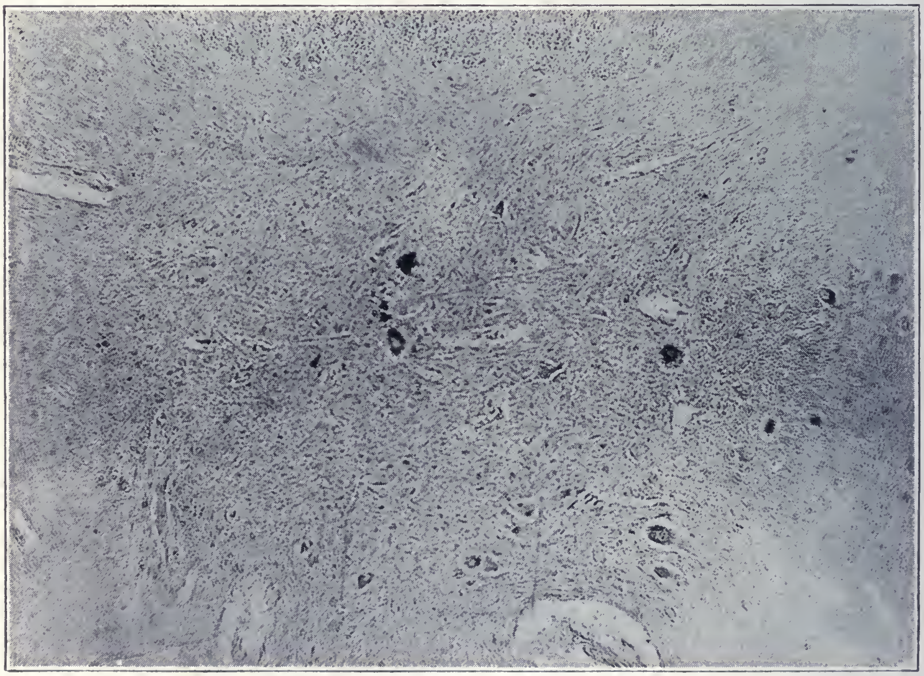


Fig. 9 (× 125).—An enlargement of area *b* (anterior or motor horn in preceding figure (Figure 7).





Figs. 10 and 11 (× 125).—Similar enlargements from the anterior (motor) horns of lower cervical and upper lumbar regions, respectively.

peripherally displaced nuclei. Comparison of the number of these cells, iarge and small, found in a series of sections, with the number of large (motor) cells found in central sections from normal cords, shows a close correspondence in the toal number of cells present.

It is doubtful if the glia cells are anywhere increased in number. The cells lining the central canal are of normal arrangement and appearance. Sections stained for neurofibrils (Beilschowsky technic not satisfactory) show possibly some diminution in the number of these elements in the gray matter of the anterior horns.

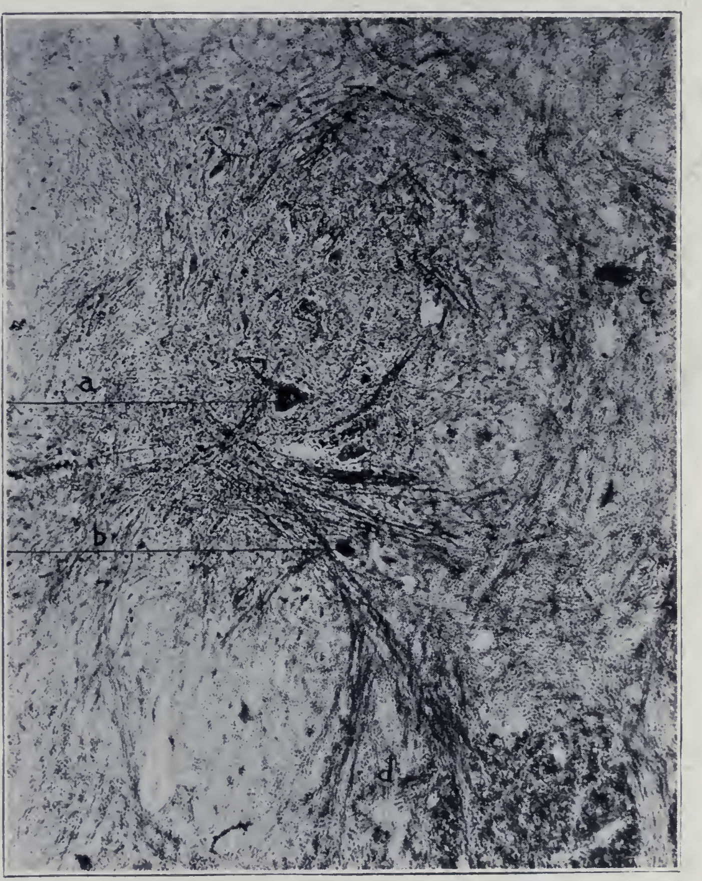


Fig. 12 (× 125).—Similar enlargement from the anterior (motor) horn at the level of the carda equina (section in this case being stained by Weigert-Pal method, hematoxylin counterstain). Shows (a) large anterior horn cell of normal structure, (b) a similar smaller cell that at the same focus appears pyknotic but is, in fact, of perfectly normal appearance, with centrally placed vesicular nucleus and well defined nucleolus, (c) an artefact, foreign matter, and (d) myelinated fibers passing out to the (right) anterior root.

The sections (Weigert preparations) that include portions of the anterior and posterior roots show that the posterior roots are much better myelinated than the anterior roots. The myelinization of the latter is, however, uniform in individual fibers. There are no degenerative changes seen.

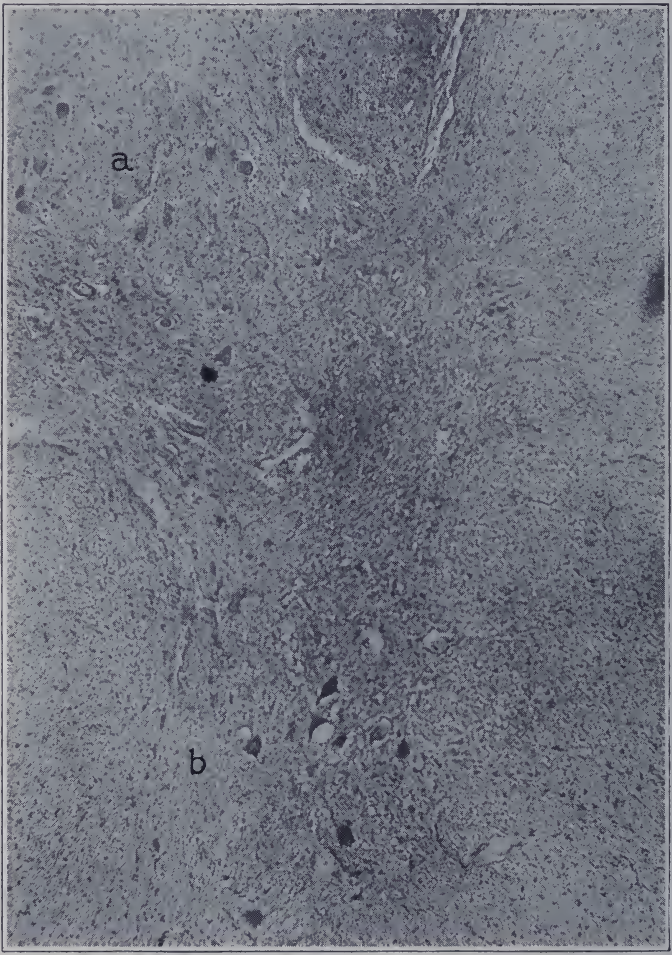


Fig. 13.—Seventh thoracic segment of cord of normal 3 months old infant, × 125. Hematoxylin and eosin stain. Shows cells of Clarke's column (a) and of anterior (motor) horn (b). Included to show comparative size of cells in these areas in normal cords. Contrast with condition obtaining in preceding figures.

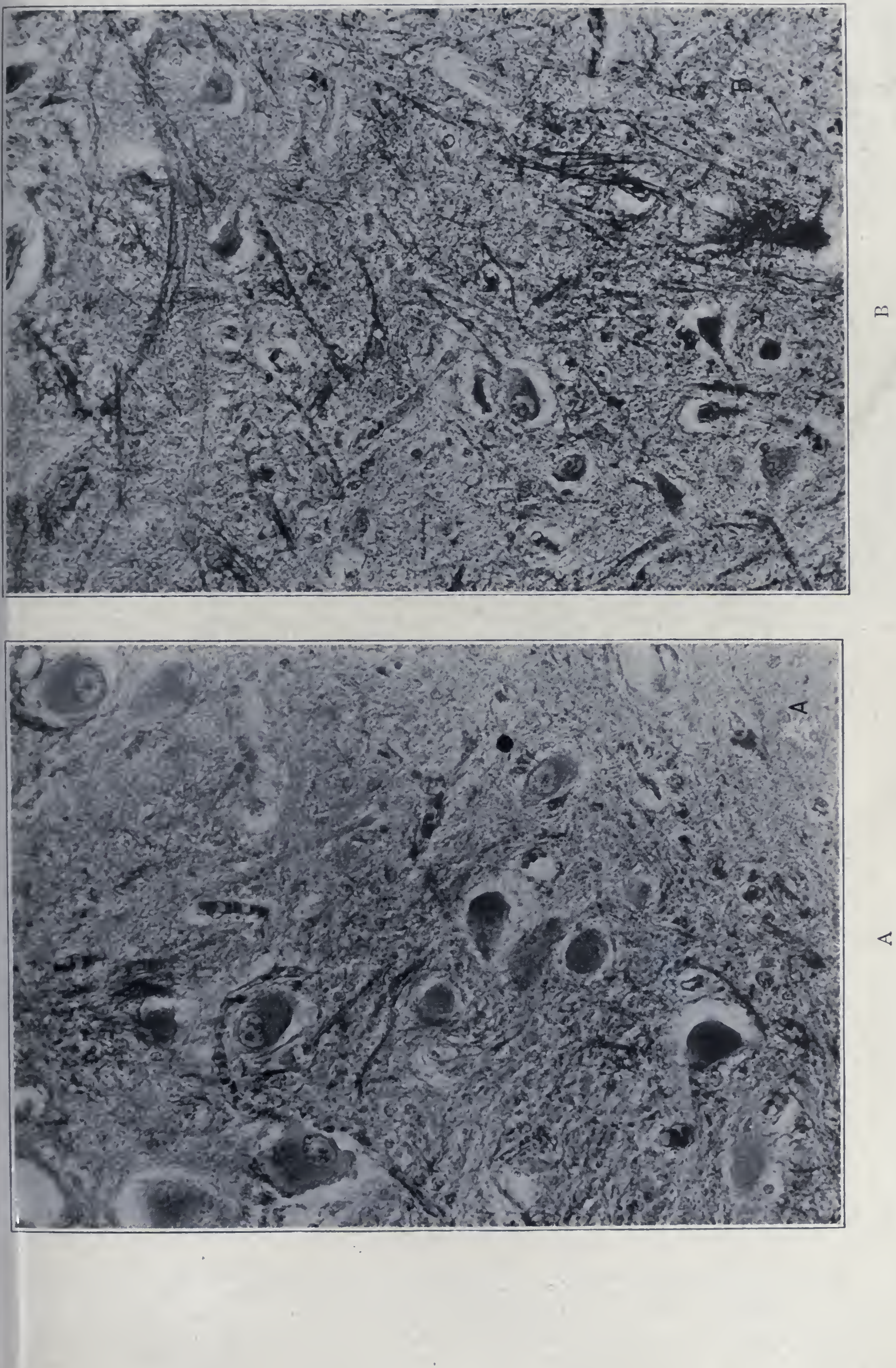


Fig. 14.—Areas from Clarke's column (A) anterior (motor) horn (B) of seventh thoracic segment, × 500. Weigert-Pal technic.

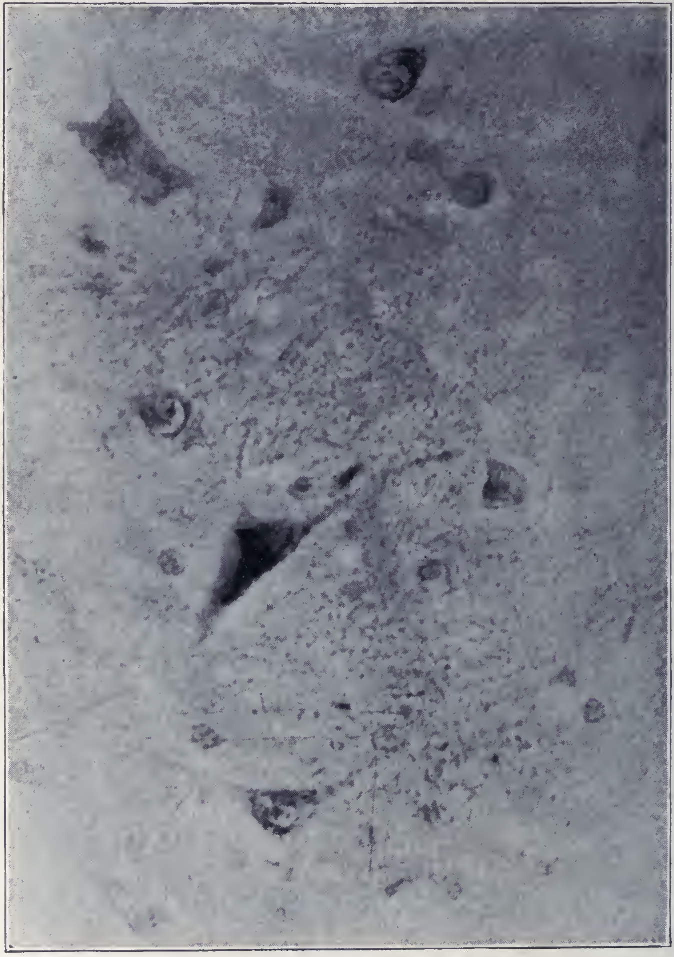
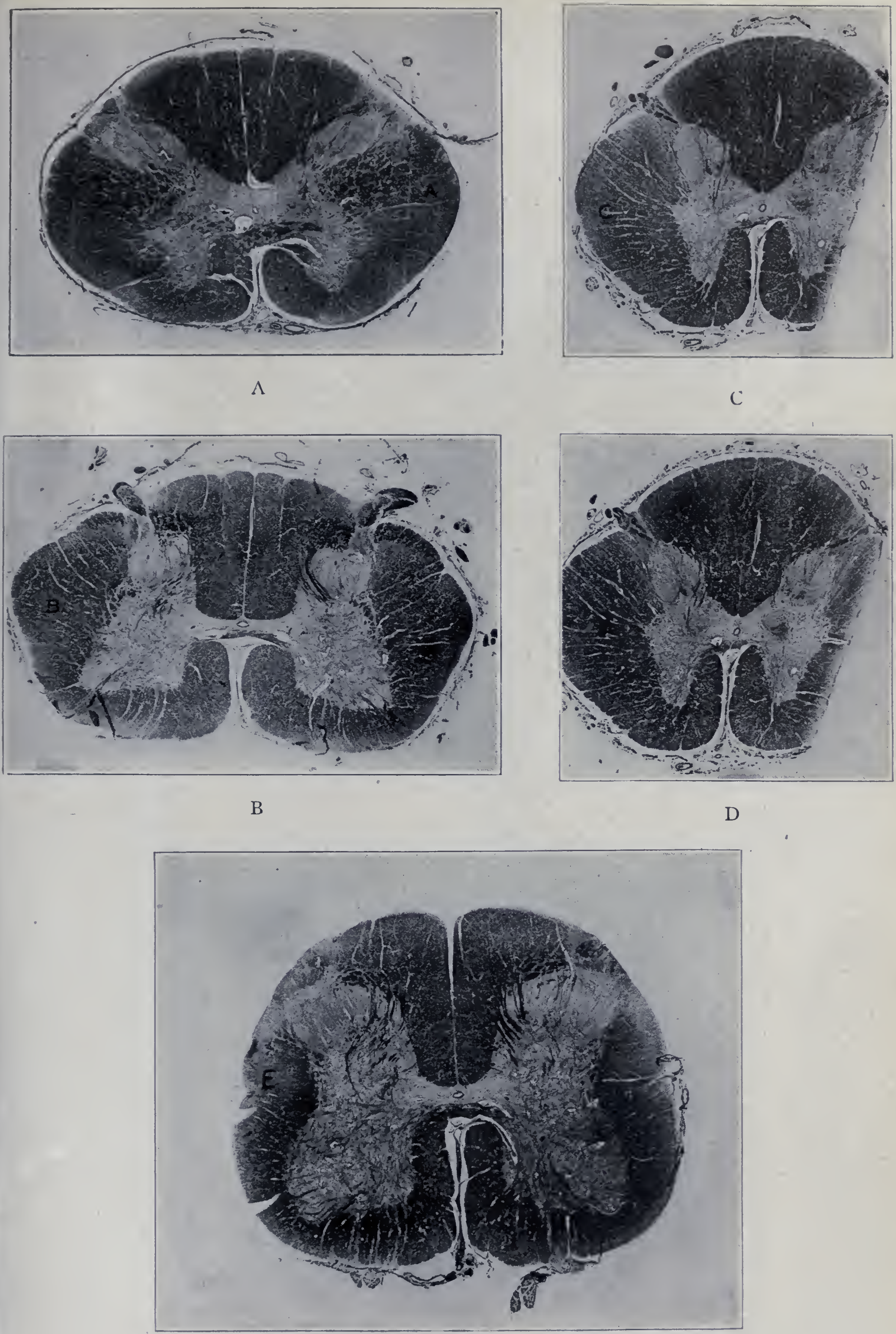


Fig. 15.—Seventh thoracic segment, × 1,000. Thionin stain. Shows character of small cells found in anterior (motor) horn. These cells replace for the most part the larger motor cells found in these areas in normal cords. c.f. Figures 9 and 14 B.



A C B D E

Fig. 16.—Weigert-Pal preparations (× 16) showing degree and distribution of myelinization of the cord essentially normal for fourth (fifth) month of age. (Relatively deficient myelinization of the anterior roots is shown in the sections from the lower thoracic and lumbar regions, where portions of the roots happen to be included. A and B, cervical; C and D, thoracic; E, lumbar.

Nothing abnormal is seen in cellular stains of the peripheral nerves, longitudinal and cross-sections (Figs. 17 and 18). The cells of the neurilemma

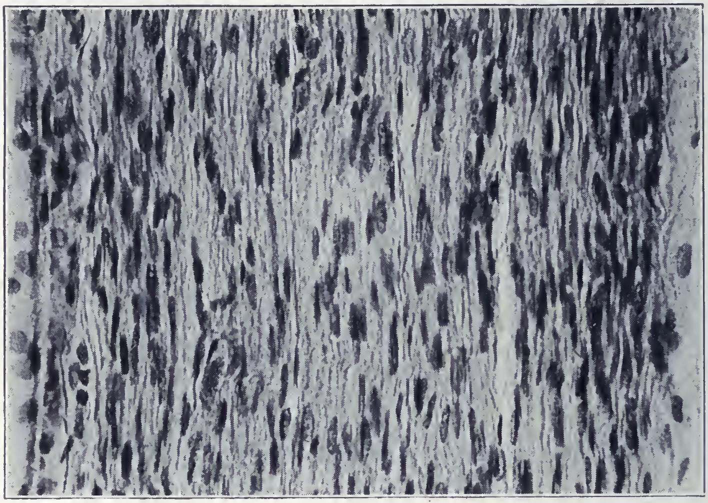


Fig. 17.—Sciatic nerve, longitudinal section, × 350. Hematoxylin and eosin stain. All cells appear healthy; no evidences of degeneration seen.

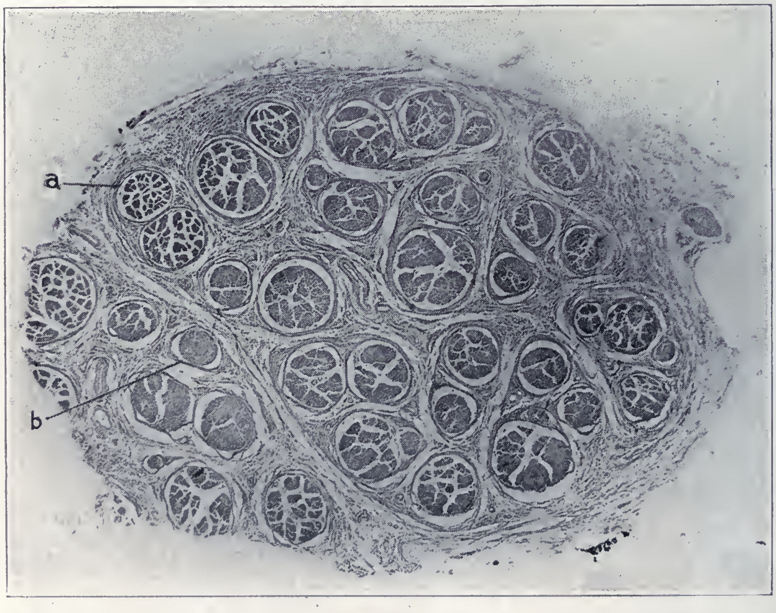


Fig. 18.—Sciatic nerve, cross section. Separation of the bundles (a) is due to technical procedures and contraction; no proliferation of connective tissue is present. The normal appearance is seen at (b).

sheaths are numerous; there is no increase in connective tissue elements. The accompanying photographs illustrate the points referred to.

Muscles: There exists a great difference between the sections taken from the diaphragm and those taken from the peripheral muscles. Sections taken from the latter all bear a great resemblance to one another.

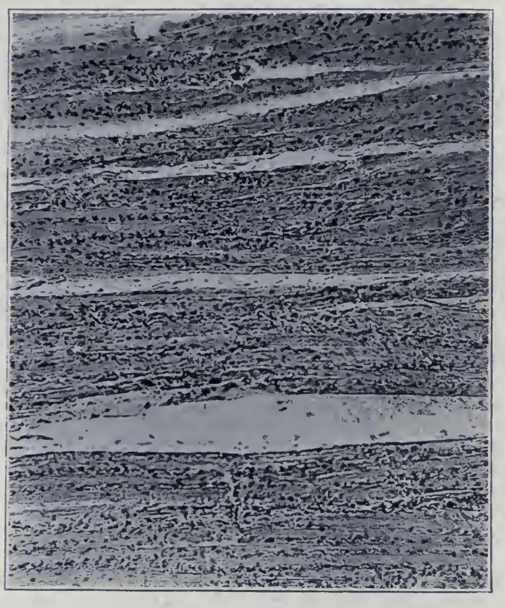


Fig. 19.—Diaphragm, longitudinal section, × 100.

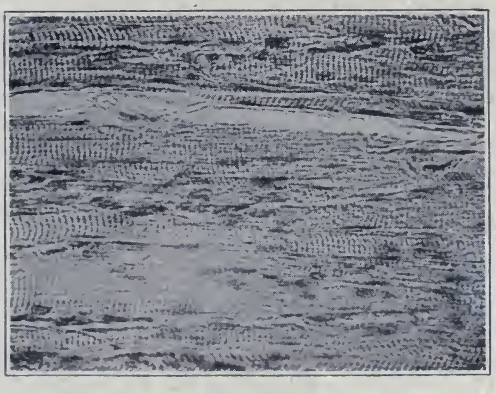
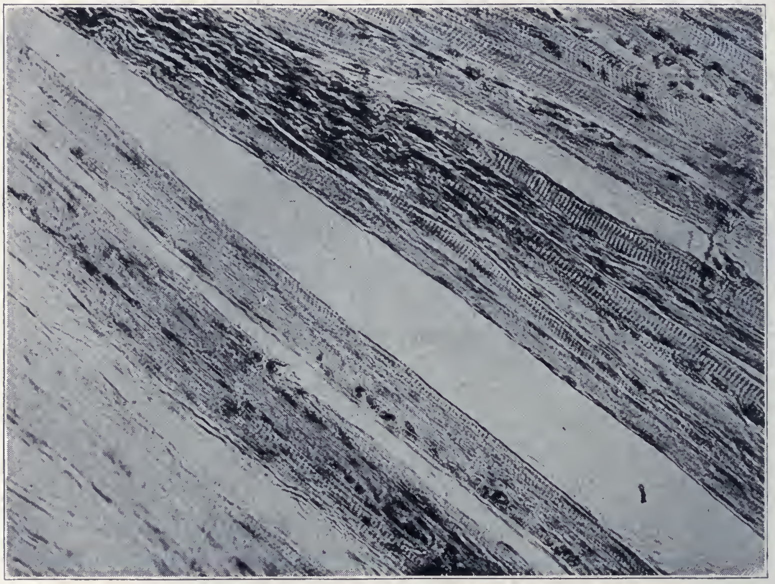
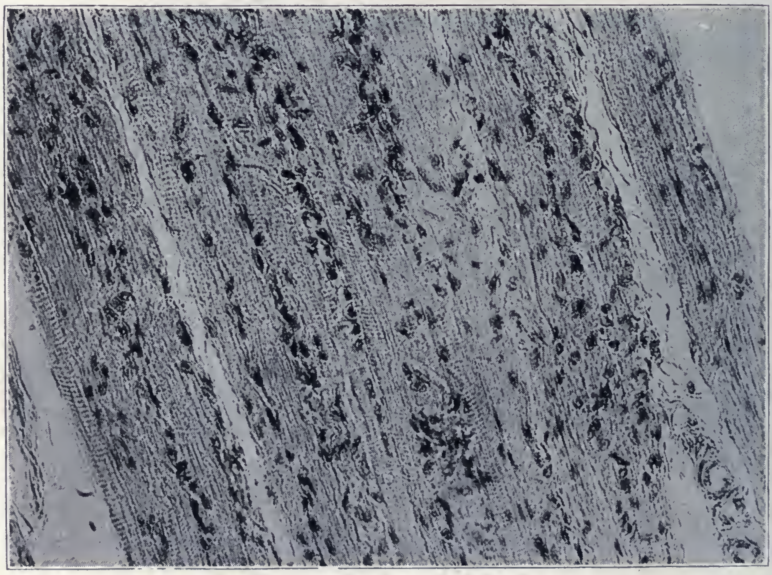


Fig. 20.—Diaphragm, longitudinal section, × 350. Showing uniform size of fibers, preservation of cross-striation, and absence of increase in number of nuclei.

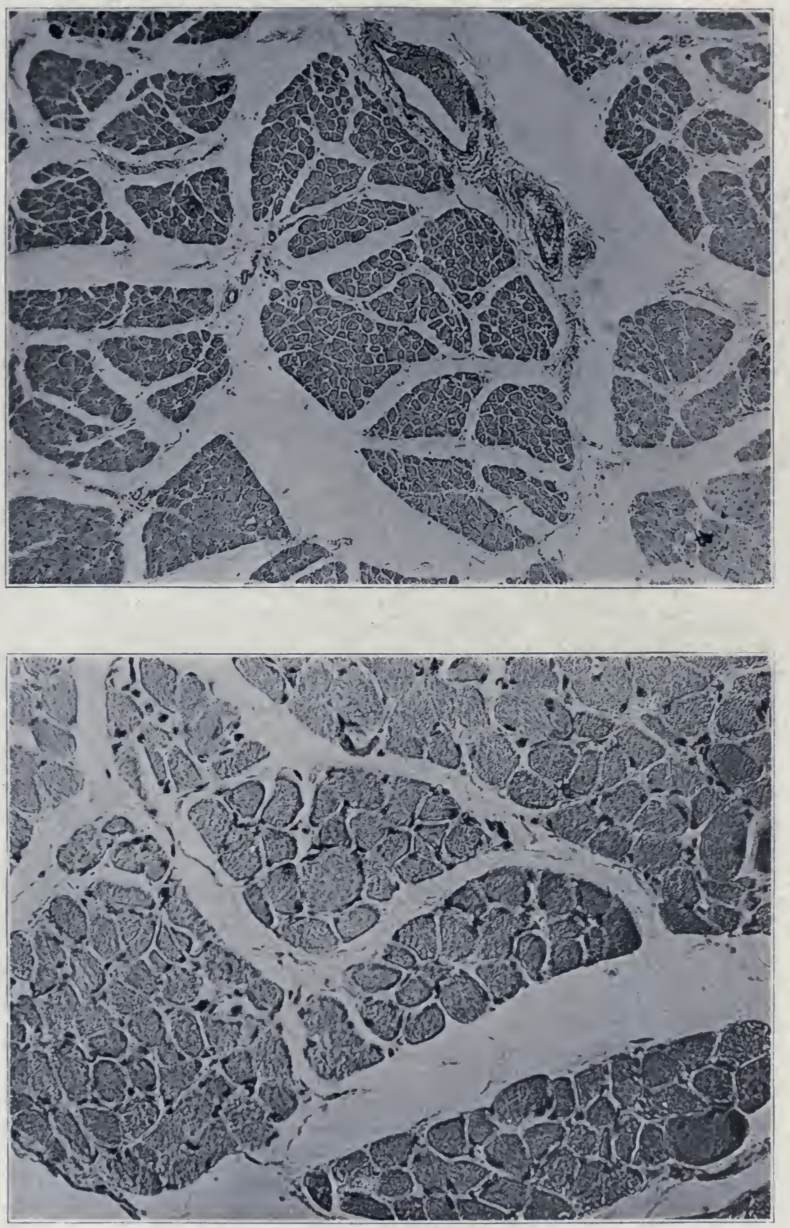
In sections from the diaphragm (Figs. 19 and 20) the fibers are normally disposed, are of approximately the usual size, and present no anomalies of striation. The nuclei appear to be normal and are not increased in number.





Figs. 21 and 22.—Diaphragm, longitudinal sections, × 400. Showing fibers in their course, and also a point of insertion into tendinous attachment.

There are no deposits of pigment, and no increase in connective tissue elements. Vacuolization and deposits of fat are not seen. On cross-section the appearance of the fibers is normal (Figs. 23 and 24).



Figs. 23 and 24.—Diaphragm, cross section, × 100 and × 400. Showing normal character of fibers as seen in cross section; also absence of increase in connective tissue.

Peripheral (Voluntary) Muscles: The picture here is a striking one. The condition is best seen in Figures 25 and 26, less well in the other longitudinal pictures. In Figure 25 it is seen that there are areas of large muscle fibers, cut in cross-section, and areas of other very small muscle fibers gathered into bundles or fasciculi. The areas of a highly cellular nature are likewise discrete. They lie scattered among the bundles of large muscle fibers as if they occupied the position of certain muscle bundles.

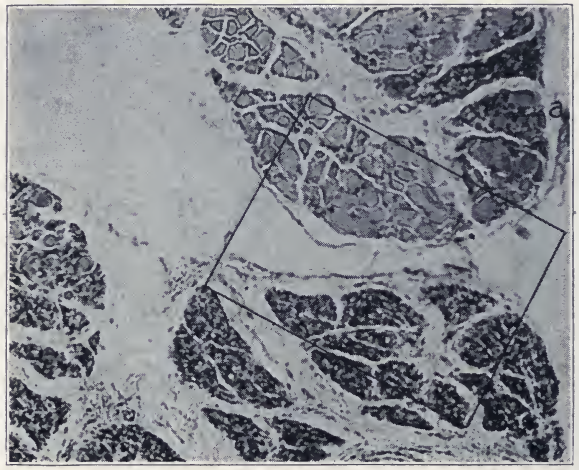


Fig. 25.—Biceps, cross section, × 100. Showing juxtaposition of sharply defined areas (bundles) of large ("hypertrophied") muscle cells and areas of small (undeveloped) muscle cells. The occurrence of bundles of mixed fibers is seen at (a).

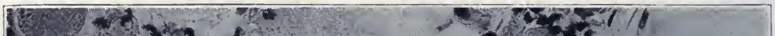


Fig. 26.—Enlargement of area outlined in Figure 25, × 400.

Examinations of the fields or areas of large muscle fibers shows that the individual fibers are much larger than those taken from the same muscles in subjects of about the same age. They are larger than fibers found in control sections from persons ranging up to 5 months of age. The areas of Cohnheim are well defined. The fibers appear to be merely hypertrophied.

The distinction between the areas of large cells and the areas of small cells is sharp. The variation in diameter seen among the large fibers is not relatively greater than seen in the control sections. Intermediate stages between the large fibers and the structures seen in the cellular areas are rarely to be distinguished.

The longitudinal sections from the peripheral muscles are all essentially similar. Their appearance is well shown in Figures 27 to 34, inclusive. Fields of large and unusually perfectly formed muscle fibers are interrupted by areas of a cellular character.

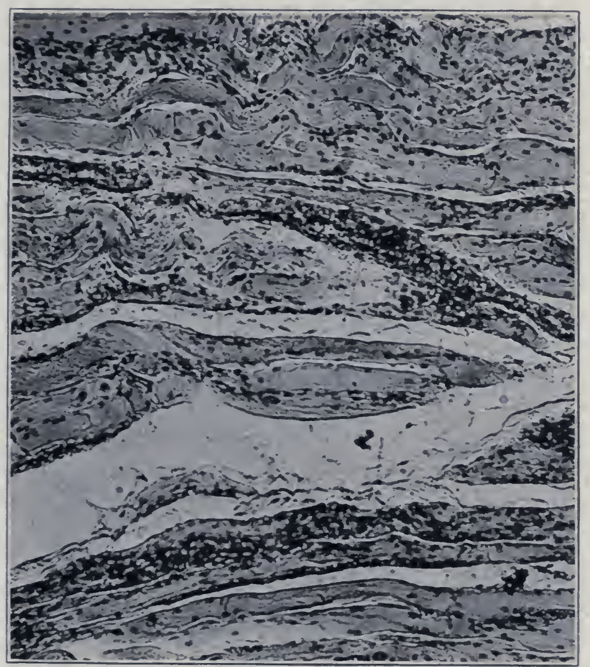


Fig. 27.—Biceps: longitudinal section, × 100. Showing what at first sight appears to be variation in size of fibers, distortion of fibers, and accumulation of nuclei in apparent course of fibers. These seeming abnormalities, however, are not real. The preservation of cross striation in all places is rather well seen.

It is not always easy to follow individual fibers for any great length. Instead of being linear, individual fibers, and more often groups of them follow a curved, sinuous or more or less spiral course.[15] For this reason many fibers are cut obliquely and frayed ends are seen. Not infrequently these overlie cellular areas and at first glance have the appearance of merging into them. More careful study shows that they do not do this and indicates that the large muscle fibers are of normal structure throughout.

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[15] This seems to be due to contractions of tissue during life and to prolonged fixation.

(There are, however, two anomalies present, both of which appear to be artefacts. The first is the occurrence in course of fibers of areas in which the sarcostyles are separated one from another and bowed to one side; occasional muscle nuclei are seen adherent to displaced bundles of sarcostyles. This seems to be an artefact due to technical procedures, found also in some of the sections from control muscles. The second anomaly is the appearance of a glassy, structureless, or finely granular material occupying short segments of some fibers. This condition is found also in certain of the control sections, and is said to be produced by the action of weak acids on muscle during the course of preservation and technical manipulation.)

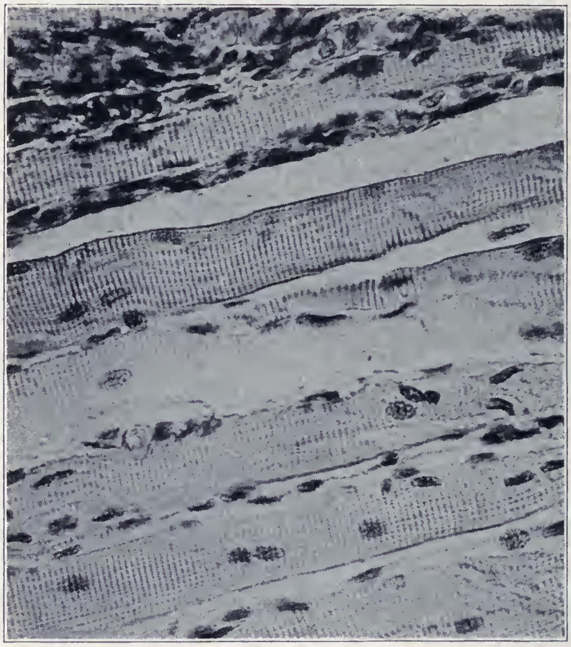

Fig. 28.—Biceps: longitudinal section, × 400. Enlargement from Figure 14 to show character of apparent increase in nuclei.

Apart from these apparent artefacts, the muscle fibers are faultless in structure, but of unusually large size for the age of the child. They have the appearance of being merely hypertrophied muscle fibers. No degenerative products whatever are seen within them.

The cells composing the cellular areas have large nuclei that appear to be identical with those of the adjacent muscle fibers. They are young looking and fresh. No mitoses are seen; nor any signs of degeneration. The tissue suggests more that seen in studying embryos rather than mature bodies. The nuclei are somewhat closely placed. The outlines of the individual cells are scarcely to be seen. It is not always clear whether they are fusiform in shape, single, or multi-nucleated. It is clear that they are muscle cells, and that they are either embryonic in character and immature (Fig. 35) or are the result of some regressive process and derived from more mature muscles.

No evidence of increase in connective tissue, endomysium or perimysium, is seen. Adipose tissue is conspicuously absent. Scharlach R preparations show only occasional globules of fat, and these are normally placed.

The most striking features of the sections, as a whole, is their resemblance to vigorous fetal tissue rather than to atrophic or degenerating mature tissue.

Comment on Histopathologic Findings.—From the foregoing study, one fact seems to stand out clearly: The condition present in the muscles of this case of amyotonia congenita is not, in a strict pathological sense, a degenerative one. The usual evidences of disintegration of highly specialized tissue are absent. Cross striation is everywhere preserved. Where the muscle cells are sufficiently large to permit of individual study, their structure is faultless. There are no degenerated nuclei, no deposits of pigment, no structureless masses of albuminous material, no hyaline areas, save those obviously due to artefacts, no intracellular accumulations of fat that are demonstrable by the usual technic, and, finally, no replacement of muscle tissue by adipose tissue, and no overgrowth of connective tissue. The possibility that the conditions present are due to acute or chronic degenerative changes may be dismissed.

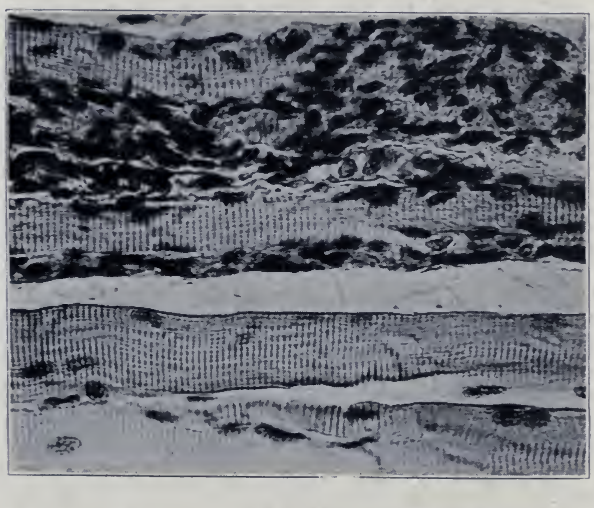

Fig. 29.—Biceps: another portion of Figure 15 enlarged to show character of increase in nuclei, × 400.

There remain two other possibilities: (1) that the condition may be due to simple atrophy, and (2) that it may be an example of retarded development. These may be taken up in order.

Atrophy.—If the condition be viewed as one of regression, or of simple atrophy, of previously existing normal fibers, two questions arise: When, or at what stage of development did the regressive process begin? and, Does the pathologic picture found here correspond to what we know of regressive change, or simply atrophy?

The only evidence we have for fixing the time of the lesion tends to show that the condition was present at birth. That the child's muscular movements were weak was noted during the first days of its life, and the weakness increased until death. That the fetal movements were felt by the mother is of little aid in fixing the date of onset, because the vigor of fetal movements, or at least the mother's perception of them, varies greatly in individual cases, and it has been shown that the vigor of movement in infants suffering from amyotonia is greater when the parts are immersed in a fluid medium. The lesion may have been present early in fetal life.

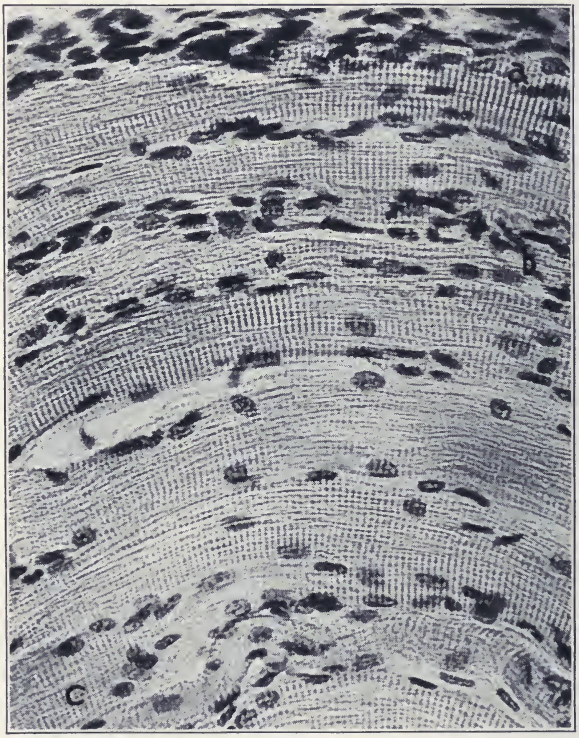

Fig. 30.—Biceps: longitudinal section, × 400. Showing (a) what appears to be increased number of nuclei in the course of a fiber with occurrence of longitudinal fragmentation of a fiber, each nucleus receiving a portion of the muscle substance in which cross striations are still present (b). Two fibers are cut somewhat obliquely at (c). This picture is capable of another interpretation—see hereafter.

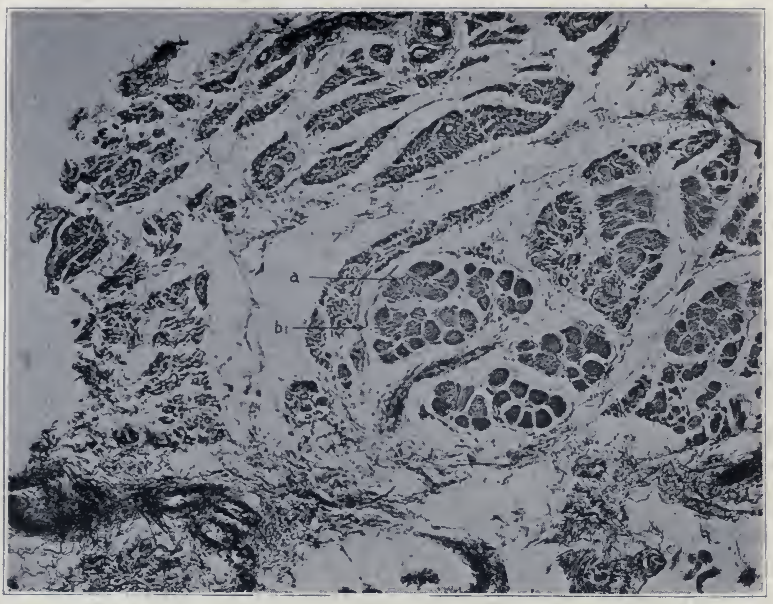

Fig. 31.—Intercostal muscles. Cross-section, × 100. Van Giesen's stain. Shows contrasting areas of large (a) and small (b) muscle fibers, and absence of connective tissue proliferation around the muscle cells. (Compare areas (a) and (b) in the center of the field.) The sharp contrast between the yellow protoplasm of the large and small muscle cells and the reddish staining of the connective tissue cells in the original preparation is not shown in the photographic reproduction.

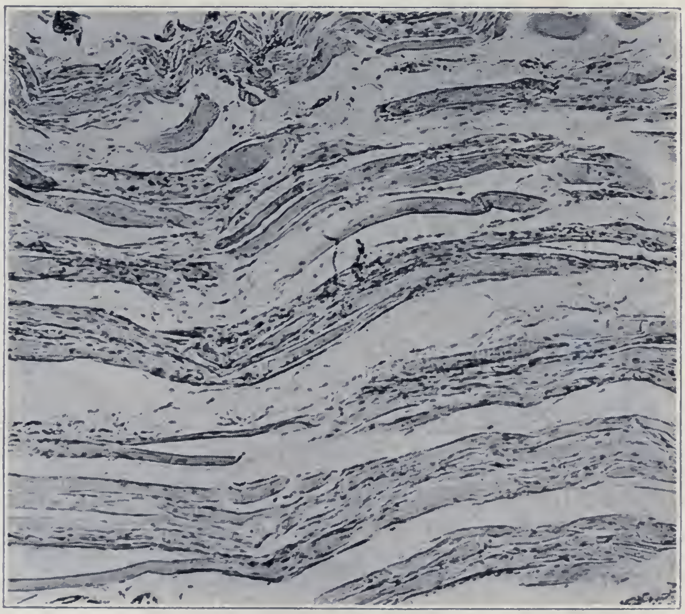

Fig. 32.—Sartorius. Longitudinal section, × 100. Showing seeming irregularities in size of fibers, absence of true increase in connective tissue, and absence of fatty infiltration. The cross striations are well preserved as is shown in higher magnifications of the same area (Fig. 24). (Absence of edema, etc., is shown by the normal appearance of cross sections of the same muscle.)

None of the accepted causes of simple atrophy appear to have been present in this case—unless it is assumed that the innervation of the muscles was abnormal and that nervous impulses of normal frequency and intensity were lacking.[16] The picture is not due to starvation with consequent atrophy. The child was merely poorly nourished, not emaciated, and during the last weeks of her life gained weight steadily. (She was, however, almost entirely lacking in subcutaneous fat.)

The histologic picture does not correspond to that found in atrophy following sudden injury to the peripheral nerves, in that such atrophy usually has associated with it evidences of true degeneration, or breaking down of highly organized substances with the production of degenerative products. These are absent. Nor does the picture correspond to that seen in cases of poliomyelitis in the very young. It differs also from simple atrophy following limitation of movement, ankylosis, cerebral injury, prolonged wasting and starvation, in that the change, while general, is not uniform in any given muscle, but affects certain fibers, or oftener, bundles of fibers, and leaves others in the same muscle uninjured, or hypertrophied. Nowhere is there seen any increase in the connective tissue elements. The delicate endomysium is not increased, indeed, considering the small size of the cells in the atrophic areas, the amount of connective tissue present, there, is less than that in the areas of hypertrophic fibers. There is no secondary sclerosis. The blood supply in the areas of small cells is not deficient; the vessels appear normal.

Delayed Development.—On turning to the second possibility, namely, that the condition present is one of retarded development of the skeletal musculature, one fact stands out prominently. The

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[16] In considering the possibility that the conditions may be due to a defect in innervation, it is interesting to compare the findings in this case with the conditions found in a form of inactivation atrophy that occurs in infants, the pseudo-paralysis of markedly rachitic babies. The changes are not wholly unlike. As described by Strauch, the muscle changes in rachitis are "marked reduction of the caliber of the fibers, defective transverse striation, marked longitudinal striation, striking increase in the number of muscle nuclei (possibly merely relative, and due to reduction in volume of the protoplasm), lack of fatty tissue, indistinct sarcolemmal edges, and densely crowded fibers." There are several objections to assuming that the processes are alike: First, that it is not clear that inactivation atrophy in infants ever causes such marked diminution in the size of the fibers as that present in our case—though it is conceivable that it might do so where defective stimulation dated from intra-uterine life. Second, that such etiology does not account for the occurrence of bundles of markedly hypertrophied muscle fibers *within the same muscle,* and occasionally, of individual hypertrophied fibers in a bundle of immature fibers. Third, and most important, the fact that the tissue at hand has not the general appearance of atrophying tissue, but rather that of young, vigorous, embryonic tissue. This attracts all observers.

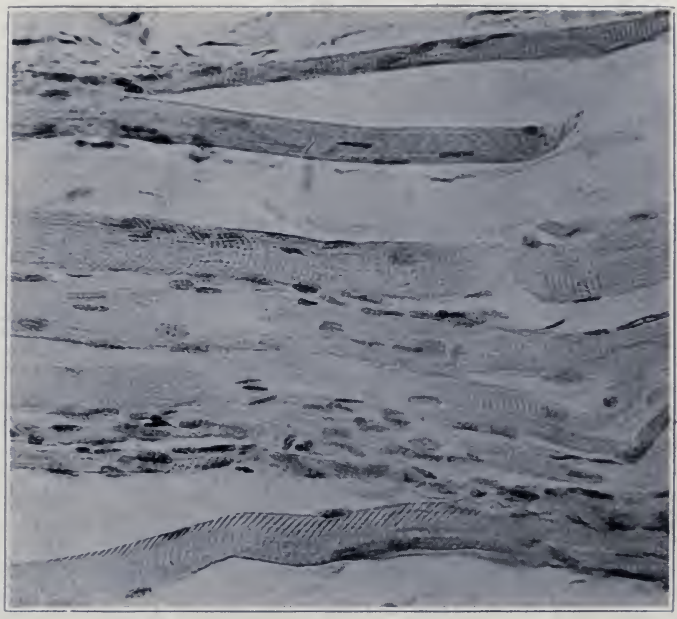

Fig. 33.—Sartorius. Longitudinal section, × 400. Enlargement from Figure 32, showing the character of the changes present in the fibers and the preservation everywhere of the cross striations.

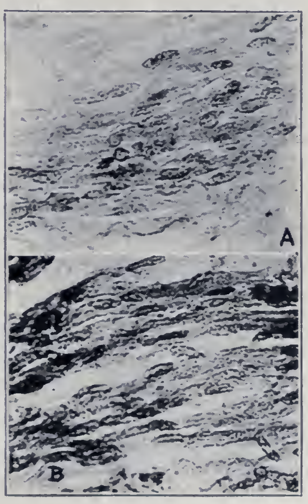

Fig. 34.—Portions of small fibers from the biceps (A) and intercostal (B) muscles, respectively, cut longitudinally and showing the fusiform character of the cells, × 400. Van Giesen's stain. (In the original preparation, the protoplasm of the cells is stained yellow; the interlacing delicate connective tissue fibrils of the endomysium stand out in sharply contrasting red (fuchsin staining). The color content of the preparations makes it impossible to obtain sharply defined photomicrographs in high magnifications. Figure 35 shows a portion of the biceps (Field A). (Drawn by Mr. Broedel from the original preparation.)

microscopic preparations from the muscles in this case bear, in the areas of small fibers, a striking resemblance to embryonic tissue. This feature at once impresses all observers. The resemblance is more than superficial.

The cells, when seen in longitudinal or obliquely cut sections, appear uniform in size, their nuclei are similar, the connective tissue element, the endomysium, is not evident. The whole appearance is that of homogeneous, healthy, embryonic tissue. It resembles most closely skeletal tissue from human fetus in the third month.

When stained with von Giessen's stain, the protoplasm takes the yellow color of sarcoplasm, and is sharply differentiated from the connective tissue filaments that are present (cf. Figs. 34 and 35). In cross sections, a delicate endomysium is seen to surround most of the cells.

In close proximity to these areas of small cells, or fibers, are found larger fibers, as already described. They conform in every detail to the appearance of mature muscle fibers. In cross sections it is possible to find every gradation from small cells with only a delicate rim of protoplasm (and this stained yellow with von Giesen's stain) up to cells of normal size and appearance, and so to immensely hypertrophied cells; in longitudinally cut sections this is not so easily done.

The entire absence of products of recent regressive change (degeneration), on the one hand, and of sclerosis, or reaction on the part of the connective tissue elements, on the other hand, speaks strongly against the occurrence of either recent or early degenerative changes. There is no evidence of replacement of muscle tissue by adipose tissue; rather does adipose tissue appear to be present in unusually small amount for an infant of this age.

SUMMARY

The case here described conforms in all essential details to the condition known as amyotonia congenita (Oppenheim). The disease was present at birth. There was no lasting amelioration, and the child died of the usual pulmonary complications at the age of 18 weeks.

The significant lesions are found in the spinal cord and in the muscles. The spinal cord is relatively large for the age of the child; the anterior roots are diminished in size as compared with the posterior roots. There is no disturbance of the contour of the cord in cross section. Microscopic examination shows complete absence of any acute, or chronic, inflammatory process, and no evidence of recent degeneration. Myelinization normal. Cells of Clarke's column of normal size and well preserved.

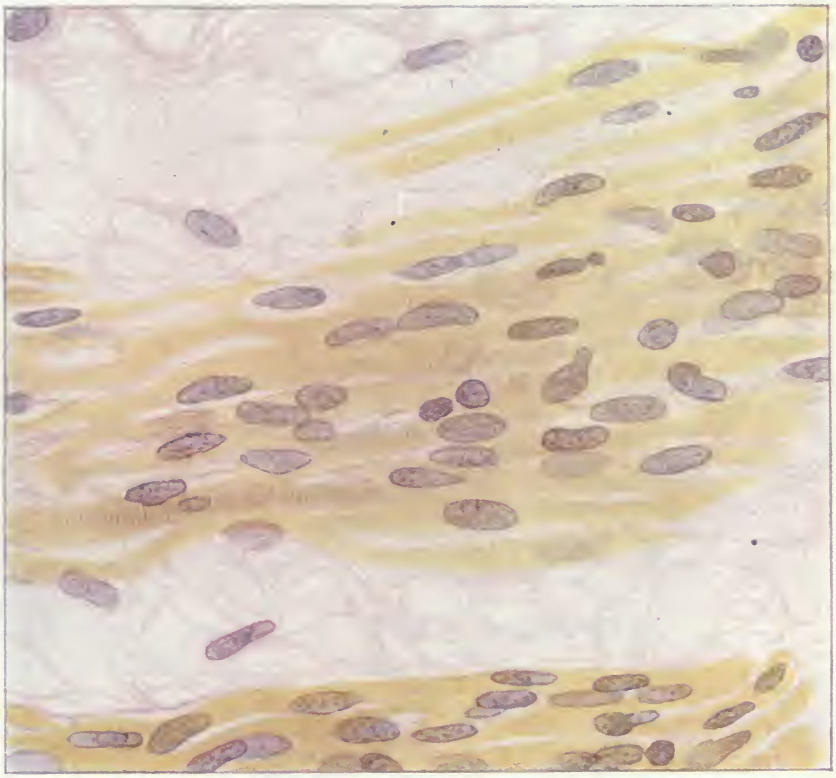

Fig. 35.—Microscopic field shown in Figure 34, A. Note the yellow staining of the muscle fibers (Van Giesen stain) and the violet staining (fuchsin contrast stain) of the nuclei and of the delicate connective tissue fibrils of the endomysium.

The large (motor) cells of the anterior horns are strikingly few in number, and are in part represented by cells that are much smaller in size but otherwise of the same appearance; only infrequently is a cell of normal size found, but, save in size, such cells as are found are of perfectly normal appearance. No gliosis.

In the muscles, areas (bundles) of hypertrophied, but otherwise normal, muscle fibers are intermingled with areas of small, apparently healthy muscle fibers (cells). The latter appear to represent less fully developed bundles of muscle fibers. There is no evidence found of present or past degenerative processes; the component muscle cells are embryonic in appearance, resembling most closely muscle cells from a human fetus of the third month. There is no increase in connective tissue; no evidence of replacement of muscle tissue by adipose tissue.

The histopathologic findings are best explained on the assumption of a delayed or retarded embryologic development affecting certain motor cells of the anterior horns and certain groups of developing muscle cells (fibers). No anomaly of the peripheral nerves, muscle spindles, or blood vessels is recognized.

LESIONS IN THE MIDBRAIN

REPORT OF A CASE

J. H. M. KNOX, Jr., M.D.

BALTIMORE

Although the midbrain is one of the smallest divisions of the central nervous system, within its structure are to be found certain essential nuclear centers and great nerve paths, motor and sensory, connecting the cerebrum and cerebellum with the spinal cord and thence with the entire nervous system. It is the continuation upward from the pons varioli and comprises the two crura of the cerebrum which are surmounted by two pairs of tubercles; the corpora quadrigemina. The aqueduct of Sylvius, connecting the third and fourth ventricles, penetrates its entire length on its dorsal aspect.

Its principal nuclear structures, in addition to the quadrigeminal bodies, are the two large paired red nuclei, receiving fibers from the superior cerebellar peduncles, the nuclei of the third and fourth cranial nerves, the central gray nuclei, the small nuclei of the fifth nerve, the nuclei of the posterior commissure of the posterior longitudinal bundles and the substantia nigra. At its upper border the midbrain is in close relation to the thalamus and the geniculate bodies.

Because of its central position and of the compactness of its structure, the region of the midbrain presents a difficult field for experimental study. The changes, therefore, in this area brought about by injury and disease have furnished more important information of the function of the several elements composing the midbrain. Extensive lesions in the midbrain are difficult to interpret because of the many complicated connections involved.

The topical diagnosis of lesions in this area has been exhaustively treated by Marburg.[1] Many of the deductions from the reported cases are somewhat conjectural. It is difficult, of course, to distinguish between symptoms that may be due to the destruction of nerve tissue by disease and those which are produced by alteration in function in the same area because of the involvement of neighboring structures. From the mass of often confusing data three more or less outstanding syndromes have emerged as the result of disease in various portions of the midbrain. These are:

(*a*) Syndrome of Weber,[2] which consists of hemiplegia in one side of the body with oculomotor palsy of the other side. This results from a lesion affecting one of the peduncles, due usually to thrombosis of the basilar artery, to tumors or to inflammatory products in this region, and extending mediumly so as to compress the third cranial nerve or its nucleus.

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[1] Marburg: Wien. klin. Wchnschr. **18**:532, 1905.

[2] Weber: Med. Chir. Trans., 1863, cited by Jelliffe and White: Dis. Nerv. System, Ed. 3, p. 542, 1919.

(*b*) Syndrome of Benedict,[3] which consists of the Weber syndrome plus a tremor on the side of the hemiplegia, that is, some oculomotor palsy with a crossed hemiplegia and a persistent tremor which increases somewhat on voluntary motion. Apparently, there is some uncertainty as to the site of this lesion but it probably represents the involvement of the peduncle and the third nerve, the lesion also reaching dorsally to the red nucleus which receives nerve fibers directly from the cerebellum. If the lesion fails to involve the peduncles the hemiplegia may be absent.

(*c*) Syndrome of Nothnagel,[4] which is described as a unilateral or bilateral oculomotor palsy with ataxia of the cerebellum type. It is supposed to suggest the lesion of the corpora quadrigemina with pressure upon the superior cerebellar peduncles. Symptoms of this character are more often the result of tumor in the corpora quadrigemina or in the pineal gland.

In view of the confusing symptomatology often noted in patients suffering from midbrain lesion it will be of interest to report a case in which the symptoms were comparatively definite and the pathologic findings fairly circumscribed.

REPORT OF CASE

The patient was a colored boy, R. J. [No. 6747], 3 years of age who was brought to the Harriet Lane Home, Johns Hopkins Hospital, Feb. 3, 1915, because of "general weakness and trembling and drooping of the eyelids."

Family History.—The family history was negative; the father and mother were well; one sister and one brother were living and well; a brother died of pneumonia at 10 months. There had been no other pregnancies and no history of syphilis or tuberculosis or of any illness in the family similar to that of the patient.

Personal History.—The child was born at full term without instruments and was breast fed for fourteen months. He had measles at 18 months and pertussis at 2½ years with uninterrupted recoveries. There have been no other illnesses and no sore throat or skin eruptions. The boy's development was normal. He cut his first teeth at 4 months, walked well at 11 months and talked at 17 months. There have been no disturbances of digestion and no renal symptoms.

The patient appeared to be perfectly normal until six months before admission when he stopped crying almost completely. Nothing further unusual was noted, however, until four months afterward when it was noted that his hands would shake when feeding himself. No paralysis or weakness had been remarked up to this time. At about the same period and following a coryza the mother noticed that the boy's eyes began to droop; both sides were equally affected. The child became nervous, jumped at every noise but no other change was observed except that he did not cry. The mother thought him "as bright as before."

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[3] Benedict: Nerv. Pathol., 1872, cited by Jelliffe: Interstate M. J. **18**:819, 1911.

[4] Nothnagel: Brain (July) 1889; cited by Marburg.

Physical Examination. — When seen the child's general condition seemed excellent. His temperature was 99.6 F.; the skin was clear; his head was well formed; the circumference being 19½ inches. The fontanels were closed. No abnormalities were detected about nose, ears or throat. The teeth were in excellent condition. There was some enlargement of the epitrochlear glands.

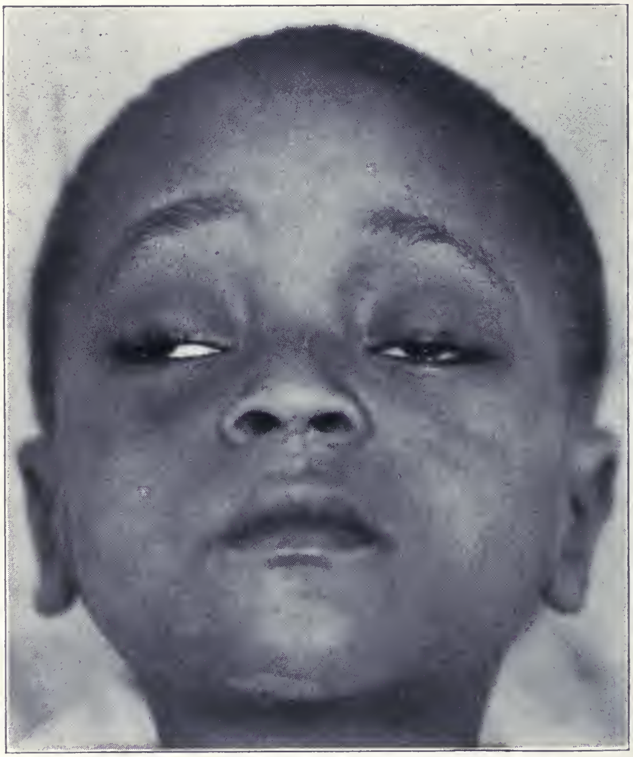

Fig. 1.—Bilateral ptosis and external strabismus of right eye due to unbalanced action of external oblique muscle.

Eyes: The pupils reacted to light, the left better than the right. There was an occasional lateral nystagmus of the right eye. A marked bilateral ptosis of the eyelids, apparently equal on both sides, was present. There was definite lateral deviation of the eyeballs to the right. Upward deviation was not well observed; downward deviation seemed normal. There was no conjunctivitis or photophobia.

The lungs, heart and abdomen presented no abnormalities. No definite weakness of the muscles of the legs or arms could be shown—sensation was normal. No alteration was found in the deep reflexes, except that those at the knee were somewhat increased. His gait seemed normal and he executed the finer movements well. Romberg's sign was absent. The boy seemed unusually bright. He obeyed commands well and was not irritable. The Wassermann reaction was negative.

Later Examination.—Two weeks later the patient returned with the history of having had two attacks of weakness (paraplegia), and that he had become very weak and limp after the second one. He was admitted to the ward, February 18. Three days afterward he became somewhat drowsy and difficult to arouse. Macewen's sign was suggestive. There was an increase of ptosis of the right eyelid which he could not raise as well as the left.

When placed on the floor, he stood with his head thrown back, arms outstretched and the feet far apart. When attempting to walk there was great uncertainty of movement and when standing or walking there was a coarse tremor of both arms and legs.

There was no movement of the eyeballs, excepting those produced by the action of the external recti. The examination of the fundi showed a very slight degree of secondary atrophy. There was no evident impairment of hearing.

Laboratory Examination.—The spinal fluid obtained was under a marked increase in pressure, gave a reaction for globulin and contained an increased number of cells mostly of the mononuclear type. On subsequent examinations the number of cells increased from 38 to 200 per c.mm. The Wassermann reaction in the blood and spinal fluid were negative. The von Pirquet test was frankly positive.

Roentgenoscopy.—The roentgen-ray examination of the head showed a moderate internal hydrocephalus and a probable tumor above the sella turcica. March 1, ten days after admission, a slight rigidity of the neck was noticed for the first time and from this time on the child grew constantly weaker. He was no longer able to support his weight on his feet. His respirations became shallow and irregular. There were slight daily fluctuations of temperature of about 2½ degrees. The external strabismus of the right eye became more marked; the ptosis continued more prominent in the right eye than in the left eye—the pupils reacted slightly to light. The ataxic movements of the hand were still noted when the child attempted to reach for objects.

The drowsiness gradually deepened. March 9, he had the first of a series of general convulsions, which continued daily until his removal from the hospital against advice March 15. No tubercle bacilli were found in the spinal fluid on repeated examinations.

He died at his home March 18, after being under observation forty-two days.

Comment.—The acquired ptosis and the curious tremor of long standing noted in the extremities and the gradually developing paralysis of the movements of the eyeballs excepting those produced by the external recti, with resulting external strabismus, occurring spontaneously in a child previously well, lead one to venture the diagnosis of tumor of the midbrain, interfering with the nuclei of the third and fourth cranial nerves. The ataxia might also be accounted for by lesion in this area, involving the red nucleus or cerebellar tracts. Toward the end there was certainly meningitis, probably of tuberculous origin, associated with hydrocephalus, although the tubercle bacilli were not demonstrated. The positive von Pirquet reaction and the subsequent development of meningitis suggested that the initial lesion in the midbrain was probably tuberculous in origin.

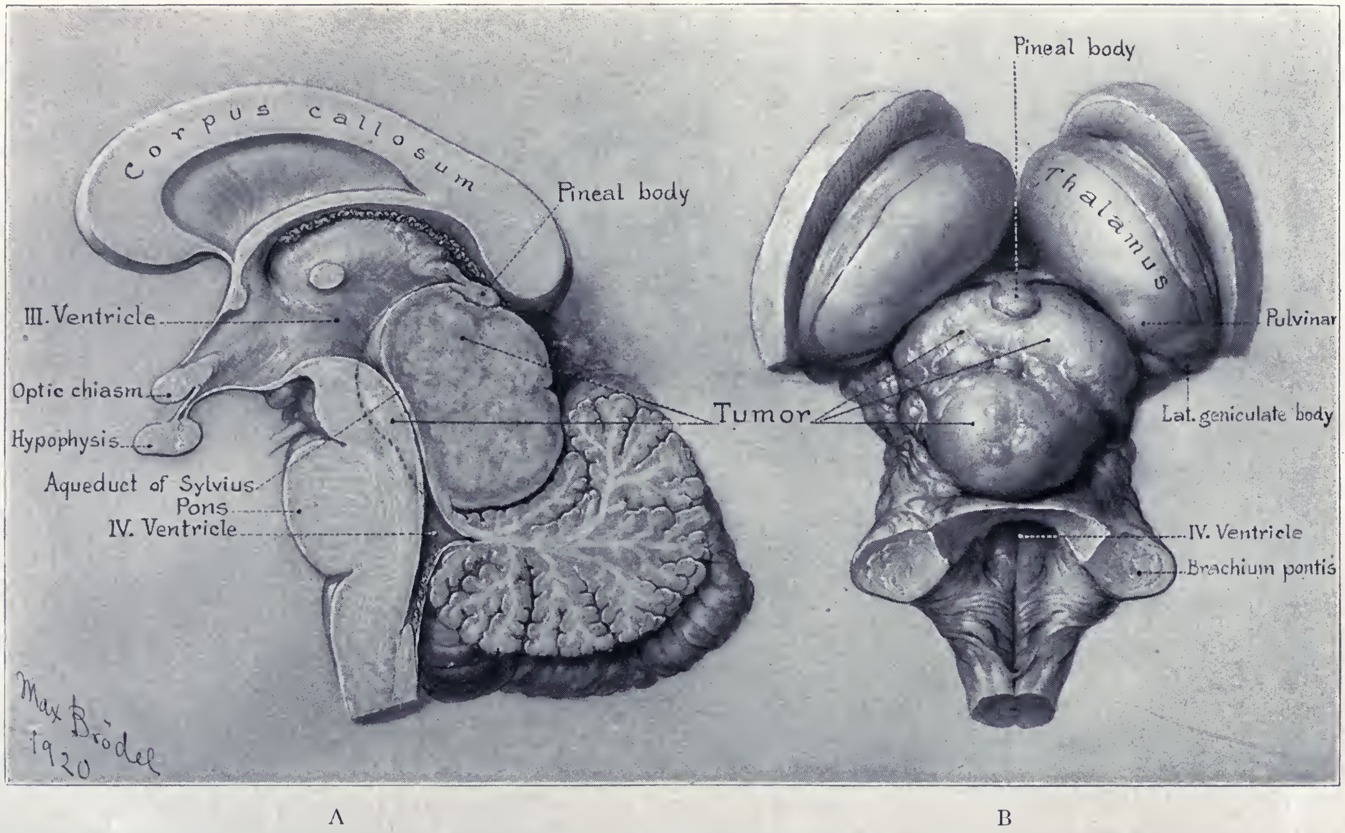

Fig. 2.—A. Sagittal section, showing the extent of the tumor, narrowing but not occluding the aqueduct of Sylvius. Most of the growth is on the right of the median line. The pineal gland is not involved. B. Sketch of the roof of the midbrain showing the displacement of the colliculi by the tumor and its relation to the thalamus and pons.

Necropsy 4310. March 19, 1915. Dr. Holmes:

A plastic exudate was found over the base of the brain, extending up to the roof of the fourth ventricle; fine tubercles were seen along the course of the blood vessels about the base and on the surface of the cerebellum. A solitary tubercle, 0.6 cm. in diameter, surrounded by a reddened zone, the whole having a diameter of 1 cm. was found in the tip of the temporal lobe. Dissection of the brain stem disclosed a large tubercle the size of a hickory nut which took the place of the upper surface of the midbrain, the colliculi. The foramen of Magendie was patent, but the surrounding cisternae were plastered down by exudate. The velum intrapositum was thickened, especially on the right.

I am indebted to Dr. Adolf Meyer for the following description, gross and microscopic, of the tumor:

REFORT ON EXAMINATION OF TUMOR

The tumor of the midbrain extends backward and inflates the whole roof so that the frenulum disappears and the two fourth nerves come out from the side of the tumor. On the forward side, the tumor has a thickness of about 18 mm., while the breadth is about 32 mm. The anterior end raises the epithalamus and superior commissure, pineal gland and pineal recess exactly 10 mm. from the transverse ridge of the posterior commissure. The midbrain ventricle is only compressed but not occluded. The whole region was cut horizontally so as to expose the third nucleus of each side.

Microscopic Description.—The tumor at a level just underneath the midbrain or aqueduct takes up nearly the whole right side of the midbrain from close to the median line to the region of the lateral fillet. In the posterior part some motor cells are preserved in tissue partly invaded by the tubercle (region of fourth nucleus) but the more anterior part of the third nucleus is invaded and completely destroyed.

The left third nucleus is not invaded, at least not in its more lateral part. There is no evidence of clean cut and limited destruction of any portion which could be made responsible for the ptosis of that side. It is more likely that we have to account for the motor restriction by pressure. Practically all the cells show dissociation of the Nissl bodies of the nature of fever alteration which reduces the possibility of distinguishing the normal and abnormal cells. Below the level just described the tumor terminates above the red nucleus without, however, invading it definitely.

In the central part of the tumor there are diffuse islands which have lost all nuclei. Only along the blood vessels are there evidences of cellular infiltration and residual tubercles. In the more superficial part of the tumor there is less necrosis and there is a fairly large number of characteristic giant cells. Tubercle bacilli could not be stained in the rather old specimen. On the surface the pia shows meningitis infiltration.

The anatomic diagnosis is solitary tubercle of the midbrain and right parietal lobe, tuberculous meningitis.

Comment.—The anatomic findings confirm, in the main, the clinical diagnosis and account for the symptoms present, although the bilateral character of the ptosis and the paralysis of the ocular muscles would have been more easily accounted for if the destruction of the third and fourth nuclei could have been demonstrated on both sides. However, a mass of the size described must exert marked pressure with interference of function in the adjacent structures not directly involved in the tumor. This fact with the well known collateral connections between the oculomotor tracts may satisfactorily account for the bilateral symptoms. In regard to the ataxia tremor, it is unwise to make any dogmatic statement in the presence of tubercular meningitis with increased cranial pressure. As, however, the peculiar ataxic tremor of the hands was noticed among the very early symptoms, it is not unlikely that they were produced by the primary lesion, the tuberculoma in the midbrain.

The general weakness and ataxic gait which came on later were probably the result of the meningitis and increased cerebral pressure.

The occurrence of tremors in cerebral lesions has been discussed by Gordon Holmes.[5] From data from sixty cases with necropsy findings he concludes that the movements are athetoid when the thalamus is involved, are chronic when the midbrain and ganglia are involved and true tremor when the lesion is in the midbrain itself.

Jelliffe[6] considers that choreiform and chorei-ataxic movements are the result of a lesion in the midbrain with the involvement of the superior cerebellar peduncles, whereas those tremors suggesting paralysis agitans arise from involvement of the red nucleus.

It would seem more probable that the choreo-ataxic tremor noted in my case might be associated with involvement of the superior cerebellar peduncles, as the growth itself did not reach the red nucleus.

Tumors limited strictly to the corpora quadrigeminal bodies must be extremely rare. The symptoms produced by a growth beginning in this area are due to the involvement of the underlying structures.

Ferrier and Turner[7] have shown that destruction of those bodies in monkeys does not result in any permanent phenomena and that the colliculae themselves apparently have a small functional value.

Among the rather infrequent cases, similar to mine in the literature should be mentioned those of Nissen,[8] who out of the large clinical material of Elizabeth Hospital, St. Petersburg, has reported five cases in which the diagnosis of tubercle of the midbrain was made and in three confirmed at necropsy. In the first case, a boy of 3 years, the principal symptoms were a gradually increasing ptosis of the right eyelid—later of both sides—oculomotor paralysis becoming complete, and a spastic paralysis of the left extremities. On section there was found a large caseous mass in the right side of the midbrain, involving the cerebral peduncle and extending nearly to the roof so as to invade the oculomotor nuclei. There was no meningitis and only moderate hydrocephalus.

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[5] Holmes, G.: Brain **27**:327, 1904.

[6] Jelliffe: Interstate M. J. **18**:817, 1911.

[7] Ferrier and Turner: Brain **24**:27, 1901.

[8] Nissen: Jahrb. f. Kinderh. **54**:618, 1901.

In the second case, a child 19 months old, certain additional symptoms were noted, namely, some stiffness of the neck and diminution of vision. These were explained by pressure in the medulla and by the extension of the caseous tumor into the optic thalamus.

The fifth case, a child 5 years old, had symptoms suggesting a tuberculosis of the brain with paralysis of both sixth nerves and optic neuritis. At necropsy an extensive tuberculous exudate involving the sixth nerves was found and complete destruction by caseous material of the corpora quadrigemina, to which no definite symptoms could be attributed.

Nissen is of the opinion that tumors of the midbrain proper tend in their earlier stages to produce only localized effects, that the general symptoms of brain tumor referable to increased intracranial pressure, such as headache, vertigo and optic atrophy, are more prone to follow tumors in other parts of the brain. He calls attention to the fact that several tuberculous masses are twice as likely to occur in the brain as is a single solitary tubercle.

Hoppe[9] has reported a case of a girl, 17 years of age, who died after an illness of a year as the result of a tumor in about the same situation as that of our patient. The principal symptoms were headache, double vision, ending in four months in total blindness; ataxia, staggering gait, paralysis of the external recti of both eyes, slight ptosis of both eyelids and atrophy of the optic nerve. There was no defect in hearing or alteration in sensation. On necropsy, a gliomatous mass, 2 by 4 cm., was found involving the corpora quadrigemina and extending back into the left cerebellar hemisphere. The nuclei of the third and fourth cranial nerves were involved but the blindness was due probably to the papilledema of the optic nerve brought about by the increased intracranial pressure. This hypertension also exerted on the nerve trunk of the sixth nerve might explain the paralysis of the external recti. This case confirms the experimental evidence and the contention of Nissen and others that neither blindness, deafness, nor ataxia are pathognomonic of the disturbed function of the quadrigemina.

Another important structure in close proximity to the midbrain must be considered briefly, namely, the pineal gland, which lies immediately upon the anterior corpora quadrigemina.

The pineal gland is the seat not infrequently of hypertrophy, tumors, cysts and various degenerative changes which may exert pressure on the subjacent structures. The quadrigeminal bodies may be flattened or destroyed and the whole midbrain greatly distorted by these masses springing from the pineal gland.

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[9] Hoppe: J. Nerv. & Ment. Dis. **39**:108, 1912.

The anatomy, physiology and pathology of the pineal body has been extensively studied. Bailey and Jelliffe[10] have collected a large series of tumors of the pineal gland and Kidd[11] in 1913 summarized all the data bearing upon the body. These writers and Skoog[12] discuss the metabolic changes which may reside in the pineal gland.

It has been claimed that adiposity and the development of premature sexual characteristics result from interference with the function of the pineal gland. The reference of these changes directly to the pineal body must be accepted with reserve, as Park[13] has pointed out that of the seventy cases of pineal gland tumors reported symptoms of precocious development appear in but five and excessive growth in but seven, and that it is quite possible that the occasional results may be due to secondary alterations of neighboring structures, as for example the pituitary.

The neurologic signs and symptoms, however, resulting from pineal tumor must be considered in discussing the affections of midbrain injury. Among them are headache, increased intracranial pressure, often with hydrocephalus, giddiness, nausea, drowsiness, isolated eye palsies, ataxic gait and tremor. It is evident that many of these symptoms are identical with those produced by primary lesions of the midbrain.

The order in which certain localizing symptoms develop is of the utmost importance in reaching an accurate diagnosis. When the early symptoms are general and attributable to increased cerebral pressure, such as headache, vomiting, optic atrophy, hydrocephalus, etc., followed, perhaps, by ptosis and oculomotor palsies, one would be inclined to place the initial lesion outside of the midbrain—such symptoms might result from meningitis or tumor elsewhere, possibly originating in the pineal gland. Whereas, as in the case here reported, the limitation of the symptoms for months to ptosis and paralysis of the oculomotor nerves and tremor without evidence of increased intracranial pressure support the diagnosis of an injury beginning in the midbrain, and as far as it goes, the absence in my case of any increased rate of growth or of sexual development suggest that neither the pineal nor pituitary glands were involved.

I take pleasure in thanking Dr. Adolf Meyer for his kindly interest and assistance in describing the specimen, and Dr. John Howland for the opportunity of reporting the case from his wards, and Mr. Max Broedel for the accurate drawings.

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[10] Bailey and Jelliffe: Arch. Int. Med. **8**:851 (Dec.) 1911.

[11] Kidd: Neurol. & Psychol. **11**:1, 1913.

[12] Skoog: Tr. Sect. Nerv. & Ment. Dis., A. M. A., 1918, p. 241.

[13] Park: Am. J. Dis. Child. **12**:477 (Oct.) 1916.

CONCERNING DIRECT SMEARS IN DIPHTHERIA *

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ST. LOUIS

It is interesting to note how widely divergent have been the experiences of clinicians concerning the usefulness of direct smears in diphtheria, and singularly so to compare the statements in textbooks on bacteriology and pathology to those appearing in books on pediatrics and medicine, for although the former are in accord that a smear suitably secured and stained will, in a large portion of cases, perhaps in half or more, furnish good evidence of the presence of diphtheria, such a belief, although to be found, does not commonly appear among methods deemed suitable for the physician.

The inherent difficulty, it seems, lies in the fact that grown on living tissues, the diphtheria bacillus appears in a great variety of forms, and that these take stains indifferently well and are, therefore, not so readily distinguishable as when obtained in culture. Everyone who has attempted to find them knows that this is true, and that because of this fact the method may well deserve its reputation for unreliability and unpopularity. If one is to make a diagnosis by the recognition of these various and varying forms he must possess a degree of familiarity with them not usually attained by any but those engaged more or less exclusively in this sort of work. So in the present study we decided to ignore all these types with which none of us were overly familiar and sought to determine whether in direct smears some readily distinguishable form would repeat itself sufficiently often to make search for it suitable to laboratory routine for clinicians not possessed of special technical training.

About seventy cases of diphtheria furnished the material, and a group of nondiphtheria throats about equal in number were used for controls. Specimens were secured from the membrane itself rather than from its surface, and this was done because in the formation of a diphtheritic patch, diphtheria bacilli are more often caught up in it than pushed up on it. The patch in diphtheria is formed, it is said, less by these organisms than by the toxins which they produce, and the presence of the bacilli in or on or beneath the patch appears to be largely haphazard and accidental, but as it forms, and destroyed cells are caught up in the exuded fibrin, these bacilli are very likely to be enmeshed and may be sought out in nests or clusters which have

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* From the Department of Pediatrics, Washington University School of Medicine. Read at a meeting of the St. Louis Pediatric Society, May 21, 1920.

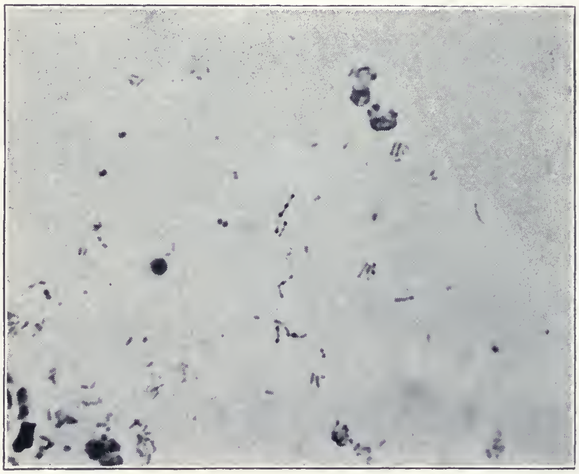

Fig. 1.—Polar bodies obtained by direct smear from a case of diphtheria on the third day of the disease. Greenthal's stain.

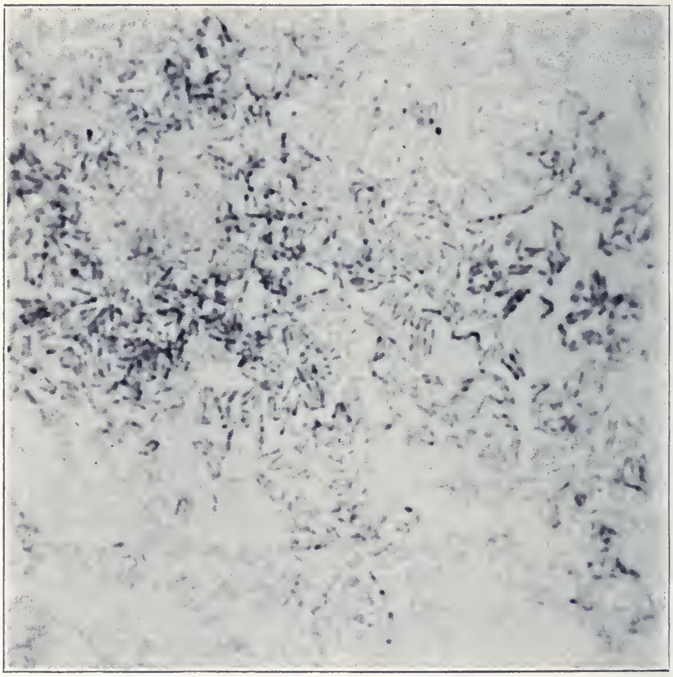

Fig. 2.—Nine hours' culture from the same case.

multiplied in situ as on any suitable medium. Because of this fact it has been advised that bits of membrane be detached with forceps and crushed between cover slips in the hope of finding these clusters. This method is said to be quite successful by those who have used it. Something of this plan was followed, therefore, forceps being replaced by a rigid scoop because easier to manipulate, a small ear curet with slightly beveled edge so as not to push the patch about, being used. This was scraped directly into the patch here and there, and several specimens from different parts of it were secured, or at times it was slipped beneath the patch and stroked back and forth over an excursion of a centimeter or more to break through the arcades by which the diphtheritic patch is customarily attached to the mucosa beneath, the scoop of the instrument in this case being directed away from the mucous membrane. Several specimens were placed on the same slide, spread about without the addition of water, dried in air or over the flame and stained. Cocainizing throats, practiced at the hospital last summer in beginning this work, was not found essential and was not continued.

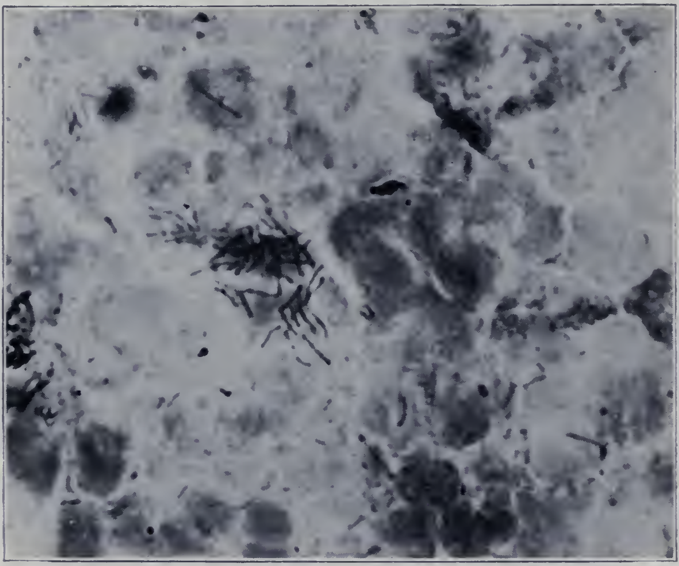

Fig. 3.—A cluster of polar bodies obtained by direct smear from a case of nasal diphtheria.

In selecting a stain, one practicable and easy to use in routine, the Neisser stain was tried and found very unsatisfactory for one not constantly using it and for physicians who do not devote a considerable amount of time to technic, it would not appear to be in any way nor for any reason the stain of choice, for any stain which by depth of shade alone can differentiate distinctly and discretely the granules from the body of this bacillus, makes it discernible with ease, without contrast of color as sought by the Neisser stain. Indeed, most other stains claim a certain contrast in color, but it was never possible in this work to identify a diphtheria bacillus granule by its violet shade as opposed to the blue color of the remainder of the organism. Of several stains tried, Ponder's and Greenthal's seemed to serve better than others. Loeffler's stain did not usually give so light a field nor so clear and distinct differentiation between granules and body as did either of those mentioned. The hanging drop of water over a well slide, as advised by Ponder, was tried and found of no material aid. This method does not, insofar as we could judge, give any better definition of the organism although slight increased magnification, because of the water, is achieved. But this magnification is not essential, as the bacillus and its granules are large enough to be seen with ease with careful focussing over a strong white light. It seemed that a No. 10 ocular gave the best results, some definition being sacrificed by this ocular, however, for increased magnification.

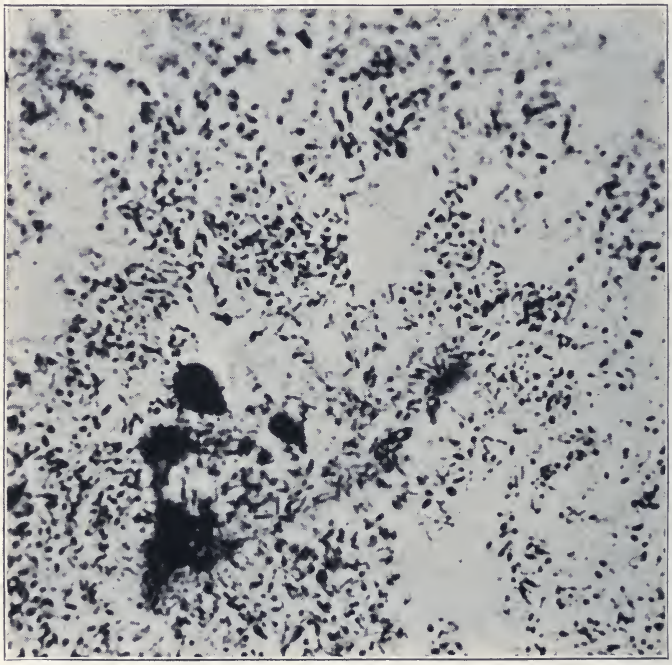

Fig. 4.—Thirty-six hours' culture from the same case.

Greenthal's stain[1] is an acid stain in which crystal violet is replaced by kresylecht violet. It was found almost impossible to use it incorrectly, which, as was said, is a very great advantage for those not devoting a great deal of time to bacteriologic work. A half minute or a minute usually suffices, but it was left on much longer at times without overstaining. Greenthal's stain, four months old, has been found still working well.

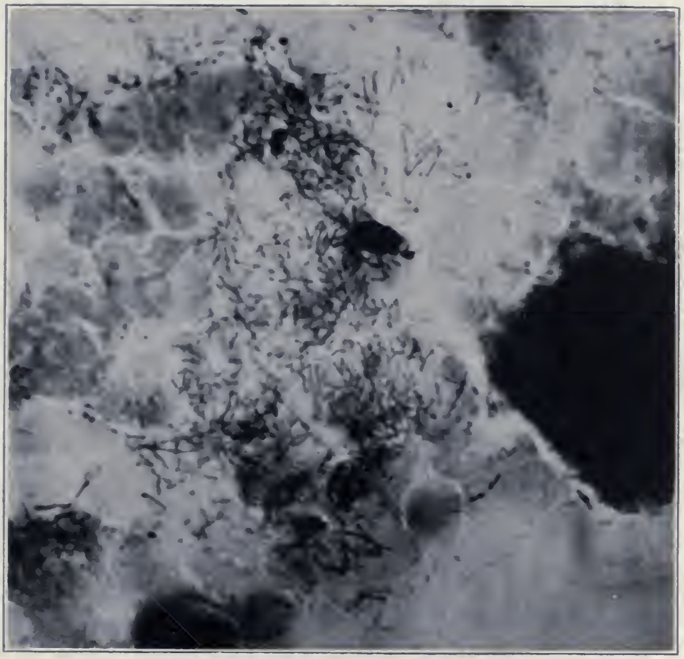

Fig. 5.—Cluster of polar bodies obtained by direct smear from a case of diphtheria on the third day.

Recognition.—Diphtheria bacilli of the true polar type, suitably stained, are said to be distinguishable from all other organisms (Park), and are differentiated from pseudotypes by their length and form and the sharpness of staining of the granules. This was learned without trouble by comparison with young cultures. The body must be stained faintly, but seen distinctly and clearly from one end to the other through their entire length. This simple precaution having been taken, it is not difficult ordinarily to distinguish the diphtheria bacillus of this

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[1] Kresylecht violet, 0.07 gm.; methylene blue, 0.10 gm.; glacial acetic acid, 3.00 c.c.; water, 100,00 c.c. These dyes were procured, as were those used by Greenthal, from Eberbach & Son, Ann Arbor, Mich. Am. J. Dis. Child. **18**:25 (July) 1919.

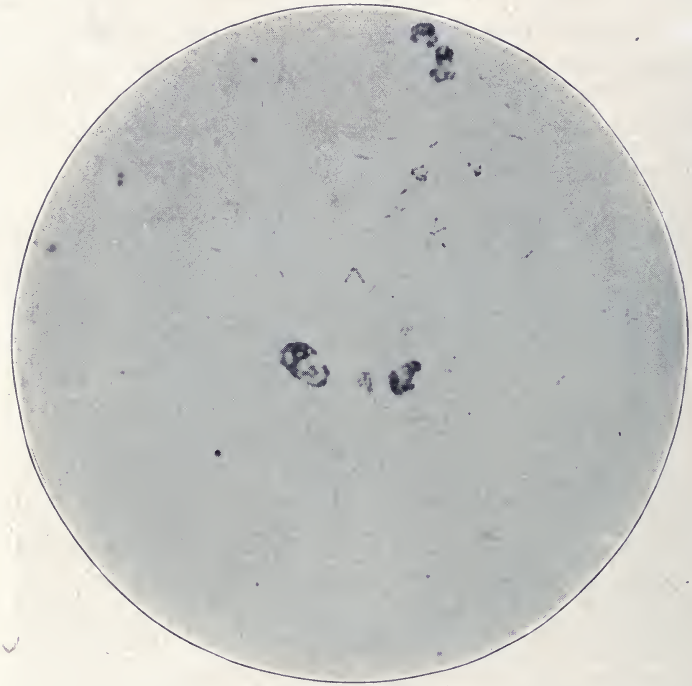

Fig. 6.—Polar bodies obtained by direct smear from a case of diphtheria on the seventh day.

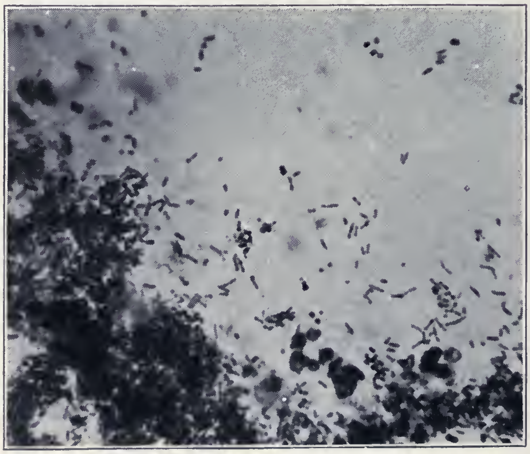

Fig. 7.—Almost pure growth of beaded and clubbed forms obtained by direct smear in diphtheria.

type from other bacilli very commonly met with which do not take the stain uniformly, and, therefore, present areas of deep staining which show as false beading and may be so recognized. By length alone there is probably a degree of safety in differentiating them from the common pseudo-bacillus of Hoffman which, taken from living tissues or in culture, is usually short. Both these precautions are costly and extravagant and would not do at all in the hands of a bacteriologist able to reckon with the true diphtheria bacillus of irregular staining and short form but it had been our experience that, were all of these included, as well as the very numerous varieties which must be helpful to him who is familiar with them all, the value of the work to us would have been nil, and we should have believed, as do many others, that for the clinician, at least, direct smears in diphtheria are unreliable and impracticable. Therefore, rather than searching for dissimilarity, we sought organisms uniform in type and indistinguishable from each other, and when these were reasonably abundant, and we were satisfied, we called them positive. Judged in this very restricted and safe way,

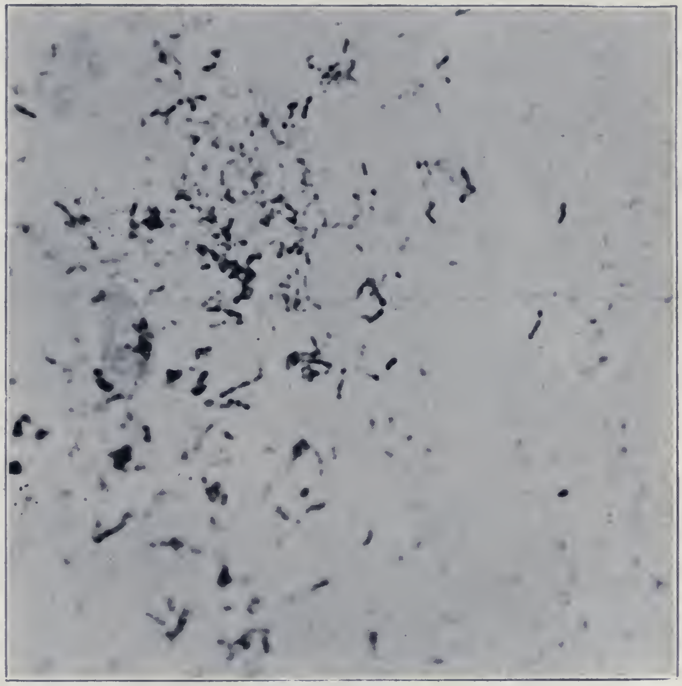

Fig. 8.—Polar bodies of diphtheria obtained by direct smear from the ear. This slide had been judged "probable" and became "positive" when photographed.

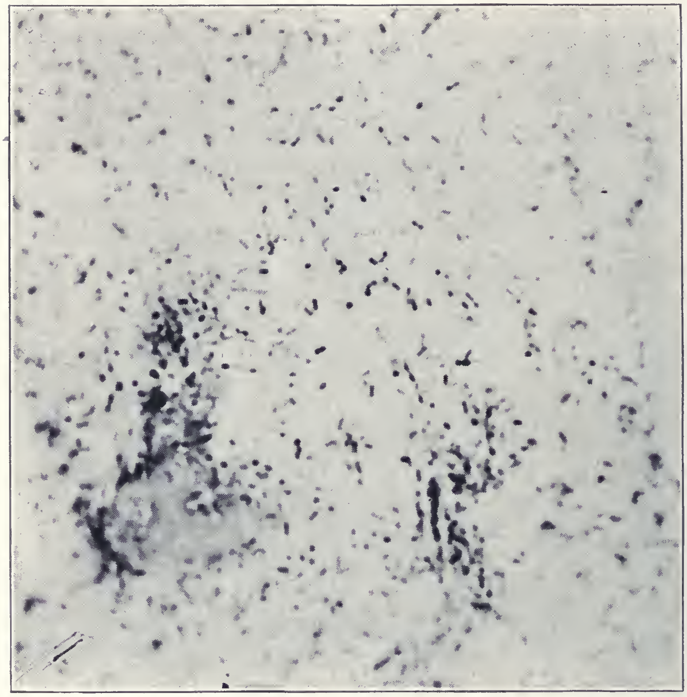

Fig. 9.—Diphtheria bacilli obtained by direct smear from a patch on the glans penis.

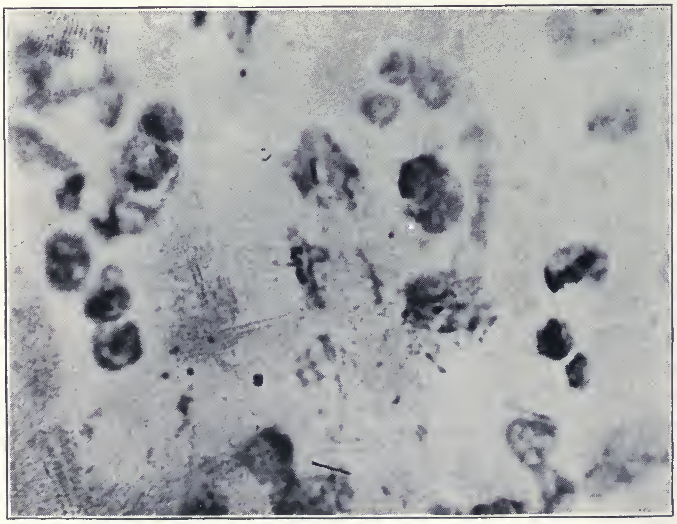

Fig. 10.—Showing that at times very characteristic polar bodies may be picked out, one at a time.

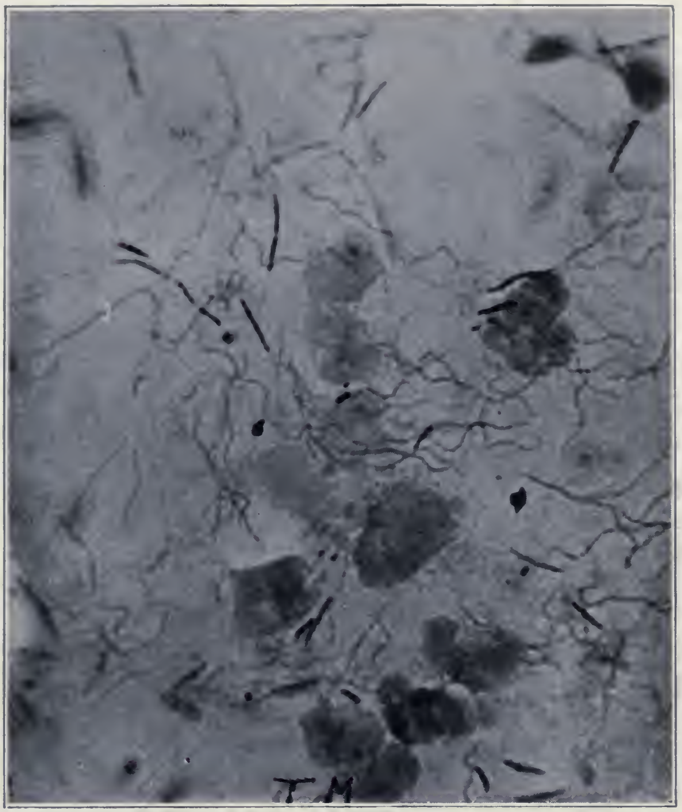

Fig. 11.—Vincent's and diphtheria coexistent.

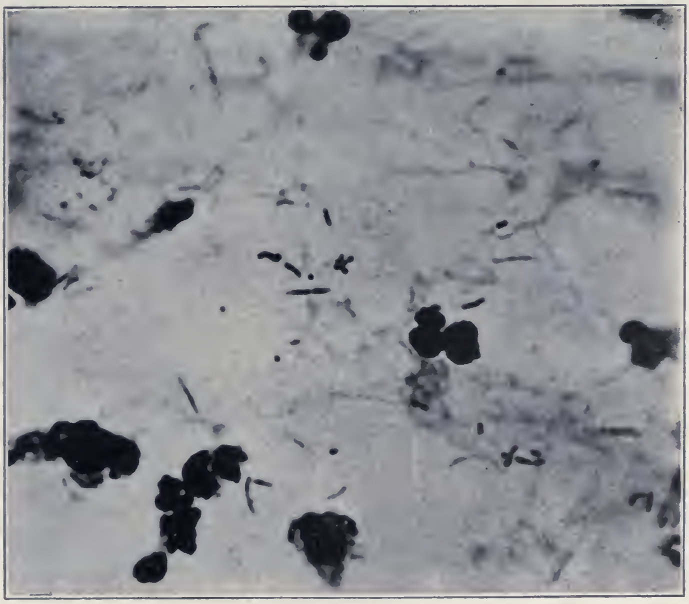

Fig. 12.—Vincent's angina and diphtheria coexistent.

we encountered, now and then, a culture of these, grown on living tissues, as numerous and as easily stained and recognizable as are those grown on media in the incubator. In the entire series this occurred in twelve cases, or 17 per cent., which is not high, but sufficiently high to make the test practicable and worth while, for there is probably no disease, with the single exception of meningitis, in which a diagnosis is at all times so urgent as in diphtheria, and if direct smears can save a few hours' time, in even this small percentage of cases, they should not be put aside altogether.

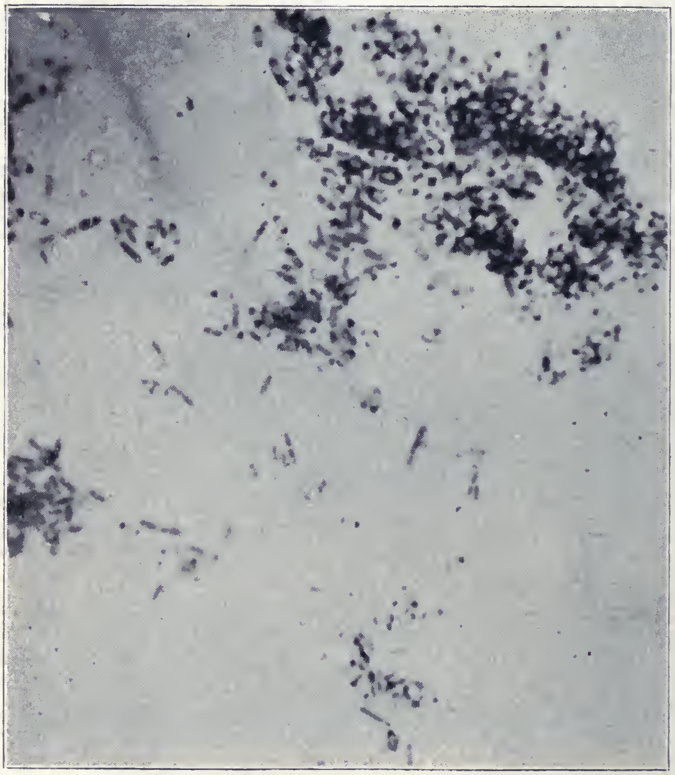

Fig. 13.—"Safety-pins," a pseudodiphtheria bacillus encountered several times in nondiphtheritic membranous sore throat.

Some of these positive slides showing diphtheria bacilli as well beaded and as readily recognizable as from any culture, have been photographed.[3] Comparison may be made between Figures 1 and 3, showing diphtheria bacilli obtained by direct smear and Figures 2 and 4, which are cultures nine and thirty-six hours old respectively.

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[3] Great credit must be given to the photographer, Mr. A. M. Obrecht of the medical school, for the excellent results he achieved in making these pictures.

Most of these slides were made from cases of diphtheria which were clinically more or less obvious but we have all seen cases of more or less obvious diphtheria which were not diphtheria, and three or four were from types in which additional information was most welcome. The duration of the disease, as well as could be ascertained, was from two to fourteen days as follows:

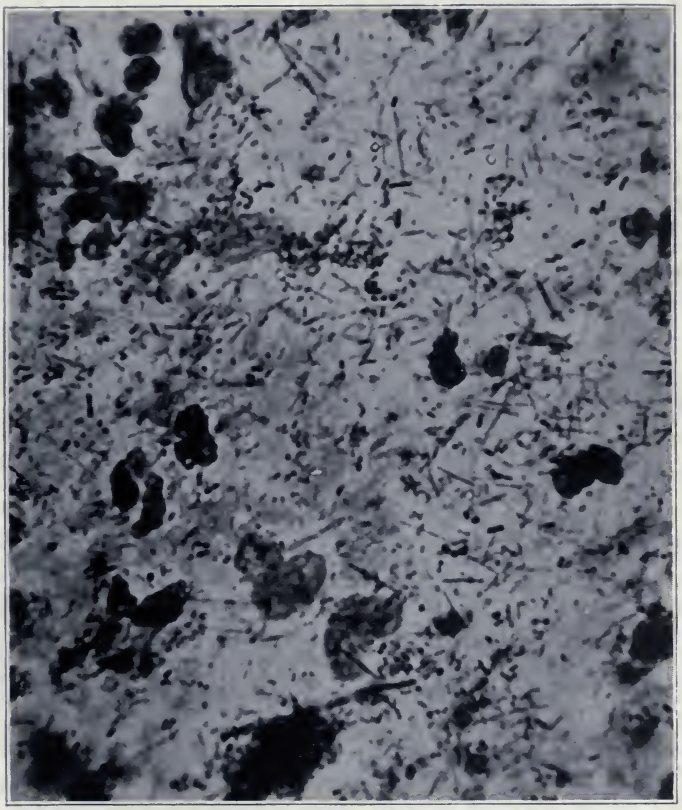


Fig. 14.—Heavily staining long bacilli, some of them beaded, beads occurring closely together, classed "negative." Occasional slender bodies, not beaded, some streptococci and other bodies.

One case on the second day.
Three cases on the third day.
Four cases on the fourth day.
Two cases on the fifth day.
One case on the seventh day.
One case on the fourteenth day.

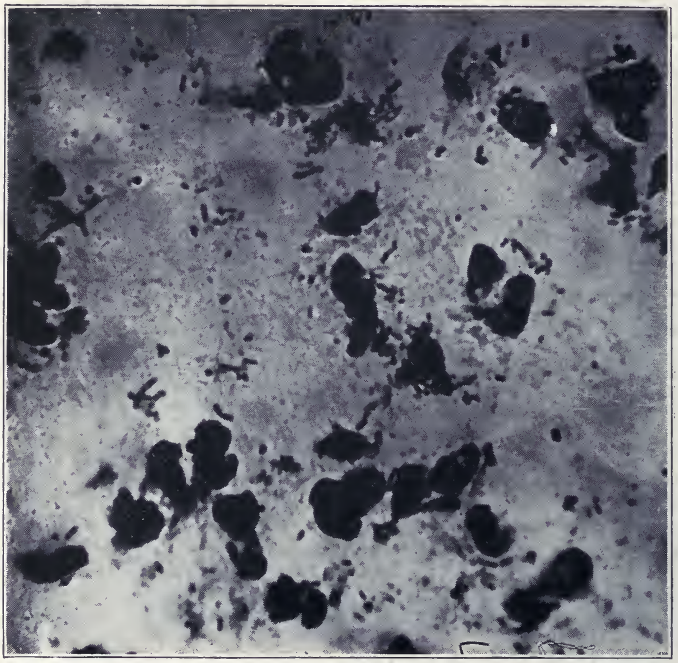


Fig. 15.—Beaded bodies resembling K-L, but because of lack of uniformity in length, thickness and beading, classed as "negative."

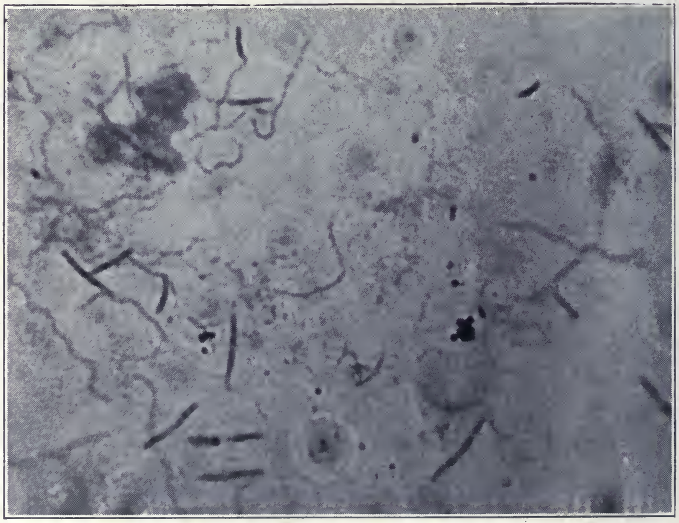
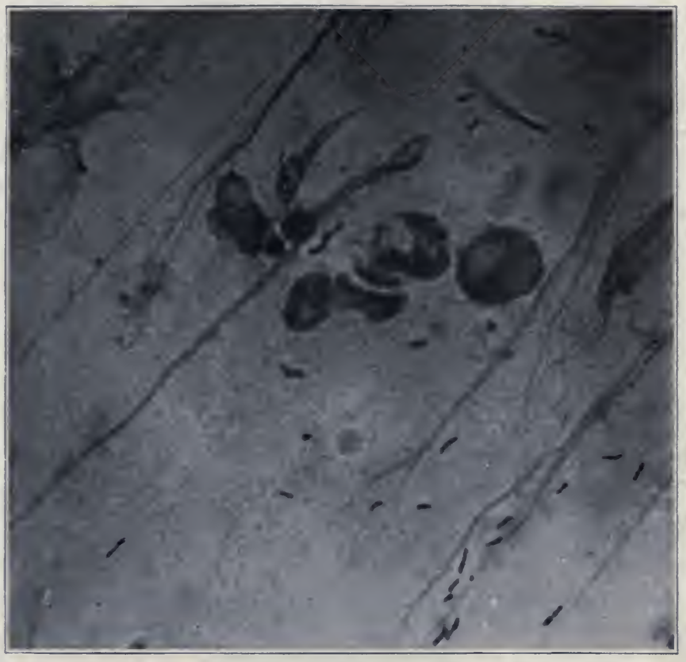
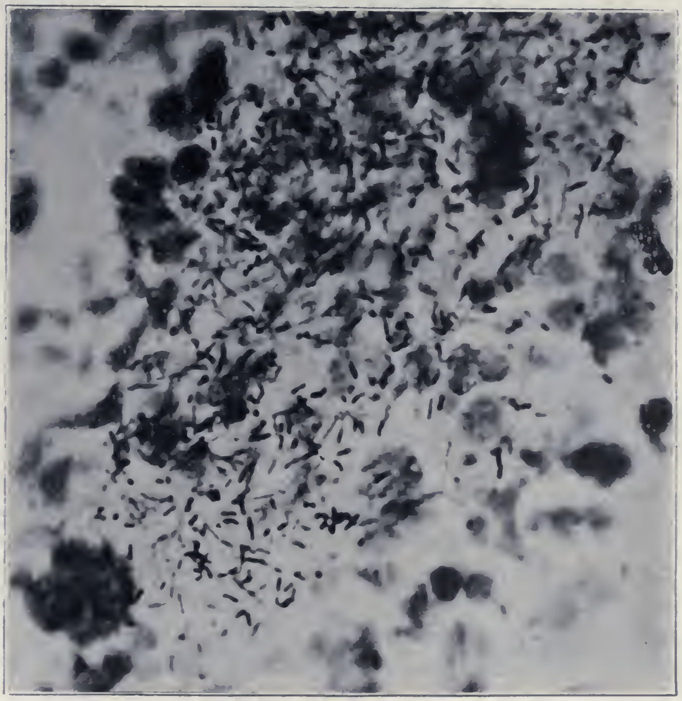


Fig. 16.—Diphtheroid angina (Vincent).



17. Large deeply staining bacilli, taking stain irregularly, one of the commonest forms to confuse one in direct smears from the throat.



18. Irregularly staining bodies not distinguishable by direct smear. In lower left corner probable K-L.

In one of the doubtful cases, there was a shreddy loosely attached patch which was not at all suggestive; two cases presented typical follicular tonsillitis, which was diphtheritic, and two cases showed sloughy patches in which Vincent's angina and diphtheria coexisted.

Probable Smears.—It was the purpose of this work to find polar bodies by direct smear in every case in which they were present. Several specimens were taken from various parts of the membrane and these were searched through with more or less thoroughness. We found that were this search continued long enough organisms which were beaded could almost always be found, and for a time we thought that prolonged search for a few or even for one or two of these more or less typical in appearance, would be as satisfactory for diagnosis as finding polar bodies in large numbers. We had to

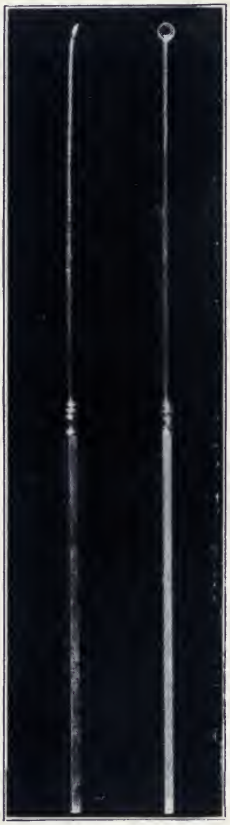


Fig. 19.—Scoop used for obtaining direct smears from a diphtheritic membrane (one-half [?] actual size).

put this aside, however, and concluded that for any but the highly experienced technician such conclusions would be very hazardous. We never quite gave up the idea that adequate searching of any direct smear might be useful and we have reserved a rather large group from among the slides which were not definitely positive which we wish to call not negative but probable. These amounted to 42 per cent. and included, among others, a form which we did not include in the positive group, namely, the short, clubbed form which Nuttal and Graham-Smith say can usually be found in direct smears. No doubt, in the hands of those familiar with the variations of form assumed by the diphtheria bacillus as it occurs on living tissues, many of these slides which we called probable would have become positive, but even we, as clinicians and not bacteriologists, may be justified in attaching a certain clinical value to such evidence just as to any clinical signs, which although present are ill-defined and uncertain but would, as any clinical signs, become less so with increasing familiarity with them.

Negative Smears.—Specimens secured from cases of known dipththeria which failed to reveal any evidence of the presence of Klebs-Loeffler bacilli, amounted to 41 per cent., and were so classed because neither polar bodies nor any other readily distinguishable form could be found. This was the group most difficult to deal with, most time consuming and, of course, unprofitable, but still we think not wholly without interest for the reason that on several occasions other conditions were discovered which could not have been found in any other way.

Figures 13, 14, 15, 16, 17 and 18 were selected from among a rather large group of negative slides to show varieties of organisms which are likely to confuse one in searching for diphtheria bacilli and whose interpretation we believe should be left to the expert.

CONCLUSIONS

In a small proportion of cases, a bacteriologic diagnosis of diphtheria can be made by direct smear as well as by culture. Contrary to widespread belief this is available to the clinician not possessed of any unusual skill or training in this sort of work and affords a simple and very exact aid to the diagnosis of diphtheria. In this series this occurred in one in about five or six cases and does not represent what might occur in the hands of another observer. Probably the unpopularity of direct smears in diphtheria is due to expecting too much of them rather than because of any difficulty inherent to the method, for if one seeks those forms with which he is familiar and trusts his judgment to no others, he is entitled to feel as sure of the opinion formed as in dealing with any organism whose morphology is currently used as an aid to diagnosis.

Thirty cents each will be paid for the following issues of the American Journal of Diseases of Children: January, 1913; February, March, November and December, 1914; January and August, 1915; January, 1918; March and April, 1919. Address to AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Ill.

American Journal of Diseases of Children

VOL. 20 DECEMBER, 1920 No. 6

SOME PHASES OF THE PATHOLOGY OF NUTRITION IN INFANCY*

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Since the chief function of the infant is growth, it is not surprising that the nutrition of the infant should be the chief concern of those responsible for his welfare. Congenital anomalies of structure, acute and chronic infections, unsuitable food, unhygienic surroundings, too much attention or too little attention, in fact, almost any factor external or internal which can affect the infant at all has an influence on his nutrition. Scarcely any one portion or system of the body may become affected without involving the general nutrition. A growing realization that it is the infant as an organic whole that must be considered, rather than any individual organ, has led to a much broader conception of diseases in infancy and to more rational therapy. This is especially true of those diseases which are associated with gastro-intestinal disturbances. The time has passed when we center our attention exclusively on the alimentary tract and allow the infant to die of a curable derangement of the intermediary metabolism. The nutrition of the infant now claims our chief attention. The gastro-intestinal tract concerns us for the reason that any alteration in its function exerts a profound influence on the general nutrition.

The great importance of gastro-intestinal diseases as a factor in infant mortality is well recognized. We know that some infants suffering from diarrhea develop symptoms suggestive of acute poisoning and succumb within a relatively short time, while others lapse into a chronic state of malnutrition which only too often eventuates in death. We also know that exactly the same symptoms may occur in the case of infants who have not suffered from diarrhea. Czerny recognized this fact and grouped the causes of nutritional disturbances under three main heads: food, infection, and constitution. Granting the importance of these etiologic factors, we are still largely in the dark as to how each of them acts, as to what causes the symptoms and even as to why such infants suffering from nutritional disturbances should die. Very little information is obtained from the necropsy room. In the great majority of instances the pathologic findings on infants dead of nutritional disturbances are essentially negative.

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* From the Department of Pediatrics, Washington University, and the St. Louis Children's Hospital.

* Read before the Harvey Society, New York, March 27, 1920.

In the absence of anatomic changes we are forced to conclude that some profound alteration in the chemical or physiologic processes in the body must have occurred. This conception has led to much investigation and more speculation as to the nature of these changes, and a popular idea has been that most of the symptoms are referable to toxic substances of metabolic or bacterial origin. Finkelstein [1] and his colleague, Meyer,[2] have especially emphasized the conception of "food poisoning" as a cause of nutritional disturbances. They consider infection and constitutional abnormalities chiefly as contributory factors in that they lower the infant's tolerance for food, that is, the ability to utilize food without the production of harmful substances. The fact that many of the symptoms are increased when excessive food is given has been the basis for this belief. An entirely different interpretation of this fact, may be made as will be seen later. Finkelstein and his assistants have made numerous attempts to determine the nature of the hypothetic poisons elaborated from food during the processes of metabolism but the experimental evidence has not been conclusive. Substances capable of producing all of the symptoms have not been found and no satisfactory explanation has been offered as to the exact mode of action of these hypothetical poisons or of the nature of the peculiar "tolerance" which permits some infants more than others to take large amounts of food without disturbance of the nutrition.

In the absence of proof of a "food poisoning" as the cause of symptoms, it would seem worth while to search for other possible explanations of the observed facts. It is the purpose of the present paper to present a brief account of such a search.

Two types of nutritional disturbances will be considered, one an acute toxiclike condition usually following severe diarrhea; the other, a chronic state of failing nutrition commonly known as "marasmus." The prominent symptoms of each condition will be mentioned and the cause of these symptoms discussed.

Striking symptoms are usually more easily explained than are less marked ones so the search for underlying causes began with a consideration of the most stormy of the nutritional disturbances. The condition referred to is known by various names such as "gastro-intestinal intoxication," alimentary intoxication," or "toxicosis." The symptoms are for the most part hyperacute but occur much more frequently in infants who have for some time been in poor nutritional condition, especially those who have suffered from previous attacks of diarrhea. Such an infant may develop diarrhea of more than usual severity. The stools increase in number and lose their normal character, becoming finally little more than brownish water passed in considerable volume, at times almost continuously. The much used term "cholera infantum" is fairly descriptive of the condition. Vomiting is frequently observed.

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[1] Finkelstein: Jahrb. f. Kinderh. **65**:1, 263, 1907; ibid. **68**:521, 693, 1908. Finkelstein and Meyer: Ibid. **71**:525, 1910.

[2] Meyer: Jahrb. f. Kinderh. **65**:585, 1907.

Coincident with the development of the diarrhea, there is a rapid loss of weight which, even in a small infant, may amount to as much as a half pound or a pound in a single day. The whole appearance of the patient changes. The features become sharpened, the eyes sunken and fixed in a far-away stare or turned upward under the half closed lids. The skin, especially over the forehead, is likely to assume a slate gray color. Over the body it hangs in loose folds; it is dry and has lost its elasticity so that it may be picked up into ridges which remain an appreciable interval before flattening out. The lips are dry, parched and often of a peculiar cherry red color. The mouth is held partly open, the tongue is dry. These infants are at first irritable and restless. There is a short, shrill cry, frequently repeated. Later the psyche becomes clouded and the infant lapses into a state of coma. Convulsions not infrequently close the scene. The respirations are deeper than normal, often of the "air hunger" type such as is observed in diabetic or uremic coma. The pulse is small, sometimes almost imperceptible, often rapid and irregular. The hands and feet are cold, although the rectal temperature is almost invariably elevated. The urine is very scanty, highly concentrated and may contain traces of albumin and a substance capable of reducing Fehling's solution. The blood is obtained with difficulty. It is thick, does not flow easily and when centrifuged separates a relatively small amount of serum. Some degree of leukocytosis is often present. There is in all marked cases a negative nitrogen and salt balance.

This clinical picture is a familiar one; it is described in some detail in order to indicate the nature and scope of the problem of determining the cause of each of the symptoms. The investigations here presented are by no means the first directed towards the solution of the problem. Various explanations for individual symptoms have been offered but in such a condition as this when a large number of symptoms are regularly and coincidentally present one must suspect some underlying cause which provides an adequate explanation for *all* of the symptoms. Obviously the problem would have to be attacked first by a consideration of the individual symptoms.

The particular symptom which has probably received the greatest attention has been the peculiar "air hunger." Czerny[3] first drew attention to this and noted the resemblance of the breathing to that of acid poisoned animals. He suggested that abnormal acids had entered the circulation. Keller was unable to find such acids in the urine. Steinitz[4] suggested a loss of base from the body in the diarrheal stools as a cause of the acidosis but the observations of Holt, Courtney and Fales[5] and of Shohl[6] have failed to substantiate this hypothesis. Dr. Howland and I[7] demonstrated by various tests that acidosis was actually present, often of a severe grade and sufficient in itself to lead to death. We found that acidosis was not the result of over production of acetone bodies and suggested that it was in part due to a failure of the kidney to excrete acid phosphate. We were indeed successful in demonstrating an increase in the inorganic phospate content of the serum and were able to show that a similar phosphate retention occurred in the case of patients suffering from uremic acidosis.[8] We believed the failure of renal function to be a result of excessive water loss from the body by way of the bowel. Oscar Schloss[9] confirmed these findings and brought further evidence of impairment of renal function by demonstrating an excess of urea and total nonprotein nitrogen in the blood, reduced phenolsulphonephthalein excretion in the urine and an abnormally high Ambard coefficient. Schloss further demonstrated that the extent of renal function involvement was, in a general way, proportionate to the degree of desiccation of the blood.

That the blood of these infants is concentrated by water loss has been repeatedly shown by various observers (Reiss,[10] Salge[11] and Schloss[9]). There is an increase in the specific gravity, in the corpuscular volume, and in the amount of dried residue. The index of refraction is increased, and the protein content high. The viscosity, the electrical conductivity and the osmotic pressure are all increased.

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[3] Czerny: Jahrb. f. Kinderh. **45**:271, 1897.

[4] Steinitz: Jahrb. f. Kinderh. **57**:689, 1903.

[5] Holt, Courtney and Fales: Am. J. Dis. Child. **9**:213 (Feb.) 1915.

[6] Shohl: Unpublished work.

[7] Howland and Marriott: Am. J. Dis. Child. **11**:309 (March) 1916.

[8] Howland and Marriott: Arch. Int. Med. **18**:708 (Nov.) 1916.

[9] Schloss: Am. J. Dis. Child. **15**:165 (Feb.) 1918.

[10] Reiss: Jahrb. f. Kinderh. **70**:311, 1909; Ergeb. d. Inn. Med. u. Kinderh. **10**:531, 1913.

[11] Salge: Ztschr. f. Kinderh., 1911, pp. 126, 317.

We know from the work of Starling[12] that with a colloidal osmotic pressure of the blood greater than the arterial pressure in the renal glomeruli, secretion of urine by the kidney ceases. This is the condition in these infants. They are virtually in a state of uremia as the result of a functional failure of the kidney.

The acidosis explains the air hunger breathing but not the other symptoms. It is in itself not usually the cause of death. It may be overcome by the administration of sodium bicarbonate by mouth or intravenously but in the great majority of cases symptoms other than those of acidosis are unchanged or may even be increased in severity and the infant succumbs. Treatment which may save the lives of patients suffering from other types of acidosis fails when applied to these infants. It is obvious, therefore, that other and more grave conditions than acidosis must be present and operative.

The clinical picture presented by these infants is in many respects not unlike that of surgical or wound shock. There is the same gray pallor, prostration, weak thready pulse and altered character of the respirations and very frequently rapidly fatal termination. The apparent similarity between the two conditions is so close that it has seemed worth while to attempt to determine whether or not some of the same factors were responsible in each.

This is not the place for a detailed discussion of wound shock; suffice it to say there is at one stage, a decrease in the amount of blood in currency, due to a passage of plasma through the vessel walls and also to the collection of blood at the periphery which is thus removed from effective circulation. This decrease in blood volume would lead to an immediate fall in blood pressure were it not for a compensatory constriction of the arterioles. In many instances this compensatory mechanism is inadequate and a considerable fall in blood pressure occurs. Diminished blood volume further results in a very greatly diminished volume flow of the blood. That is to say, a decreased amount of blood flows through a given portion of the body in a unit of time. Decreased volume flow of the blood leads to an accumulation of acid products of metabolism in the tissues and a decreased alkali reserve of the blood, that is to say, acidosis (Wright and Colebrook,[13] Gesell[14]).

The gray color of the skin, in shock, seems to be due to a stagnation of the corpuscular elements in the capillaries as a result of constriction of the arterioles. Cannon, Fraser and Hooper[15] have shown that red blood cell counts made on blood obtained from the capillaries by puncture of the skin are very appreciably higher than those made on blood taken directly from the veins.

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[12] Starling: J. Physiol. **24**:317, 1899.

[13] Wright and Colebrook: Lancet **1**:763, 1918.

[14] Gesell: Am. J. Physiol. **47**:472, 1919.

[15] Cannon, Fraser and Hooper: J. A. M. A. **70**:526 (Feb. 23) 1918.

Thus we see the symptoms of shock largely the result of a suddenly diminished blood volume. What of the infants with diarrhea who have many of the same symptoms? They too have a diminished blood volume. This, as has already been mentioned, is due to a drying out of the blood by excessive water loss.

In order to determine whether or not this decrease in the blood volume results in a diminished volume flow of the blood, we have applied the calorimetric method of G. N. Stewart.[16] The principle of this method is to immerse a portion of an extremity in a measured volume of water at a known temperature, somewhat below that of the body. The water is contained in a well insulated calorimeter. At the end of a ten minute period the temperature of the water in the vessel is measured. The increase in temperature, other factors being equal, is proportionate to the amount of blood passing through the extremity during the period of observation. The volume flow of the blood is conveniently expressed in terms of cubic centimeters per 100 gm. of body weight per minute. Dr. Kirsten Utheim[17] working in my laboratory has confirmed the accuracy of the method as applied to small animals by comparison with the results obtained by the use of the "Strohmuhr," measurements being made on the limbs and femoral arteries of dogs.

The Stewart method is easily adaptable to infants by using a vacuum food jar as a calorimeter. With proper control of the conditions we found that the volume flow of the blood in the arms or legs of infants could be determined with a very considerable degree of accuracy. It is, of course, essential that the infant should be quiet.

By the use of this calorimetric method, it was found that the volume flow of the blood in the arms of normal infants varied from 15 to 22 c.c. per 100 gm. per minute. Repeated determinations made on the same infant at different times of the day and on successive days gave remarkably constant results. In applying the method to infants suffering from the condition under consideration, a greatly diminished flow of the blood was found, this being in some instances as low as 2 or 3 c.c. per minute. In the greatly decreased volume flow of the blood of these infants we have another factor in the causation of acidosis, in addition to the failure of acid excretion, already alluded to. From what has been said regarding the nature of the acidosis in these cases, it becomes apparent why the administration of alkali alone usually fails to cure. Sodium bicarbonate, administered in isotonic or hypertonic solution, does not increase the blood volume or volume flow and does not lower the osmotic concentration of the blood, so that secretion of urine may be resumed. Hypertonic solutions, in fact, have quite the opposite effect.

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[16] Stewart: Heart **3**:33, 1911.

[17] Utheim: Am. J. Dis. Child. **20**:366 (Nov.) 1920

If the volume flow of the blood through the abdominal vessels is diminished to any such degree as it is in the extremities, one would expect that the functional ability of the gastro-intestinal tract to care for food would be greatly impaired. Such seems to be the case for it has been shown by Straub [18] that dogs rendered anhydremic by a diminished intake of water are very prone to the development of diarrhea and vomiting when fed. The same is certainly true of these infants.

Mention has been made of the presence of a reducing substance in the urine. L. F. Meyer [19] believed this sugar to be lactose or whatever disaccharid was contained in the diet. Finkelstein [20] has explained the appearance of these disaccharids in the urine as the result of a passage of undigested sugar into the circulation through the injured intestinal mucosa. Schloss,[9] on the other hand, found the sugar in the urine to be either glucose alone or glucose in combination with galactose or lactose. A certain amount of lactose can pass through the normal intestinal mucosa and it may well be the case that when fairly strong solutions of lactose are introduced into the intestinal tract of these infants that some would be absorbed unchanged. As lactose is not altered outside of the intestine, it would be excreted quantitatively in the urine. Even if occurring in the urine as claimed by Von Reuss and Meyer, the amount is too small to be considered as a factor of any importance in the production of symptoms. The glycosuria, however, requires explanation. It has been shown by Araki [21] that asphyxial conditions occurring as the result of vaso constriction, hemorrhage or a diminution of the oxygen carrying capacity of the blood, lead to glycosuria. This is generally supposed to be the result of increased glycogenolysis dependent upon acid production in the tissues. In the case of these infants the glycosuria may be readily explained on the same basis.

Diminished blood volume, such as occurs in the condition under discussion, is not necessarily accompanied by a lowering of blood pressure, such as is so frequently observed in shock. We have observed such a lowering only in exceptional instances. The high blood viscosity in these infants is likely a factor in maintaining blood pressure.

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18. Straub: Ztschr. f. Biol. **38**:537, 1899.
19. Meyer: Jahrb. f. Kinderh. **65**:585, 1907.
20. Finkelstein: Jahrb. f. Kinderh. **65**:263, 1907.
21. Araki: Ztschr. Physiol. Chem., Series of Articles in **15**: **16**: **17**: **19**.

It may be well to point out here that although a diminution in blood volume is common to the two conditions under consideration, the causes for the decreased blood volume are quite different. In the case of infants with diarrhea, there is a drying out of the blood by water loss; in shock, on the other hand, the diminished blood volume is the result of loss of plasma. The protein concentration of the serum in infants with diarrhea is high, in shock normal or low. In this difference, we have an explanation of the fact that in some instances the symptoms of the two conditions are identical, in others quite different.

That the same constriction of the arterioles occurs as a result of the diminished blood volume of these infants as has been observed in the case of shock patients, would be expected. A comparison of the red blood cell counts made on venous and on capillary bloods, showed a marked concentration of corpuscles in the capillaries. This stagnation of red blood cells in the capillaries as the result of arteriolar constriction, may well explain the peculiar gray pallor of the skin, which tends to disappear with establishment of a normal circulation.

From what has been said, it is apparent that the shocklike symptoms of these infants may reasonably be explained on the basis of the known blood volume decrease.

Constriction of the arterioles leads to a damming back of leukocytes in the capillary blood to even a greater extent than erythrocytes. For example, I have seen a difference of 5,000 in the leukocyte counts of venous and capillary bloods from the same infant. A moderate degree of leukocytosis, so often observed in patients of this type, may in part, be explained by this factor.

Fever, as has been mentioned, is commonly present in infants suffering from severe diarrhea. Suggested explanations have not been lacking. Finkelstein and his colleagues have considered the fever to be the result of pyrogenic substances in the circulation. The fact that feeding solutions of lactose or of sodium chlorid or injecting these substances intravenously, especially to infants already suffering from a nutritional disturbance, results in a rise in temperature has been interpreted as indicating that these substances may exert a direct influence on the nervous mechanism of the heat center or may so injure the cells of the body that abnormal metabolic processes are set up which result in the formation of toxic products capable of causing fever. Both salt and lactose when injected intravenously are quantitatively excreted unchanged. It is, therefore, necessary to assume that the effect observed must be of a physical chemical nature and not due to the chemical breakdown of the salt or lactose. These observations of Finkelstein on salt and sugar fever led to a great deal of controversy. A very good summing up of the literature on this point is found in a recent article by Balcar, Sansum and Woodyatt.[22] Without going into further detail, it may be stated that the weight of evidence seems to strongly support the view that the action of sugar and salt is to remove water from the body and that the effects observed after the administration of sugar and salt are the result of removal of water from the body. Woodyatt and his collaborators, in the article just cited, bring forward excellent experimental evidence that fever may occur as the result of a decreased amount of water in the body available for evaporation. They have demonstrated that the fever resulting from the administration of solutions of sugar or salts is dependent not upon the total amount of these substances given but upon the amount of water simultaneously introduced into the body. Hypertonic solutions of unutilizable crystalloids leave the body, taking with them water. In the case of the injection of isotonic or hypotonic solutions or when water is administered simultaneously to supply the water deficit there is, according to these authors, no occurrence of fever.

The infants, of the type which we have been studying, are known to have a diminished water content and a high osmotic pressure of the blood, conditions which it has been shown are capable of leading to high temperatures. That these infants show a febrile reaction and that this reaction should be increased by the administration of hypertonic solutions of sugars or salts as was shown by Finkelstein is not surprising when we consider the fact that the dehydration is thus increased. There is no need for assuming injury to body cells or the production of pyrogenic metabolites.

Water evaporation is of even greater importance in heat regulation in the infant's body than in that of the adult. Thus Rubner and Huebner [23] have shown that as much as 55 gm. of water per kilo per day may be evaporated from the body of an infant as compared with a normal evaporation of 22 gm. per kilo per day in the adult. From 30 to 40 per cent. of the total loss of heat from the body is due to water evaporation. The mechanism of water evaporation may well be considered as a safety valve to prevent increase in body temperature. Rubner and Huebner found that when the metabolism of an animal was increased by feeding meat the evaporation of water increased 48.1 per cent., while the total caloric output was increased only 27.7 per cent. When the action of this safety valve is impaired by the increase of osmotic pressure of the body fluids, fever results very much in the same way as the overheating of a gasoline engine

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22. Balcar, Sansum and Woodyatt: Arch. Int. Med. **24**:116 (July) 1919.
23. Rubner and Huebner: Ztschr. f. Biol. **38**:315, 1899.

when the radiator goes dry. Fever as the result of dehydration has been repeatedly observed in infants, in adults and in animals. Thus L. F. Meyer[24] saw it in the case of infants fed on a concentrated diet; Czerny[25] saw it in cats kept in a warm, dry atmosphere until the blood became desiccated; Jurgensen[26] observed temperatures up to 104 F. in adults undergoing Schroth's dry diet treatment.

The fever of the infants with the condition described can readily be explained on the basis of the dehydration which is known to be present. The picture is, however, often complicated by other factors. Infection cannot always be excluded. Indeed, in some instances, the presence of a parenteral infection may result in diarrhea and vomiting which leads to a dehydration of the body. Under such circumstances the fever may have a double explanation although Woodyatt suggests that even the fever of infection may be due to an insufficiency of free water in the body.

It has been mentioned that these infants during the stage of acute symptoms often excrete more nitrogen and salts than they take in. This negative nitrogen and salt balance can be interpreted only as the result of tissue destruction. That desiccation of the body results in such tissue destruction is well shown by the experiments of Straub[18] on dogs rendered anhydremic by an insufficient fluid intake. It is further of interest to note that Straub[27] has shown that the administration of salt to such animals results in a still greater negative nitrogen balance. This he interprets as the result of further dehydration brought about by the salt diuresis. Finkelstein has observed the same result following the administration of salt or lactose to infants, but has interpreted it as indicating a toxic action of sugar and salt, a conclusion with no proved basis of fact.

It has been mentioned that infants at about the time of the onset of the severe toxic symptoms suffer a loss in weight, greater than is seen in almost any other clinical condition. Losses of from one to two pounds even in the case of small infants and in a relatively short period of time are observed. This is greater than can be accounted for by anything but water loss. At the same time, examination of the blood shows a concentration which, if indicative of the desiccation of the other fluids of the body, could easily account for all of the loss of weight. The dry skin, lusterless eyes and sunken fontanel are clinical evidences of this water loss.

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24. Meyer, L. F.: Quoted from Langstein-Meyer Säuglingsernährung und Säuglingsstoffwechsel, Wiesbaden, 1914, p. 45.

25. Czerny: Arch. f. exper. Path. u. Pharm. **34**:268, 1894.

26. Jurgensen: Deutsch. Arch. f. Inn. Med. **1**:196, 1866.

27. Straub: Ztschr. f. Biol. **37**:527, 1899.

The conception presented gives us one explanation for the more frequent occurrence of the toxic states in warm weather. It has been shown[28] that an increase of external temperature from 20 to 36 C. may lead to a 600 per cent. increase in water elimination by the skin and lungs. In the case of infants with a lowered water reserve, such excessive loss by evaporation may easily lead to desiccation with its resulting symptoms. Rietschel[29] observed the development of toxic symptoms when weak infants were exposed to high room temperatures, and Finkelstein observed a lessening of intoxication symptoms when the infants were removed to cooler surroundings. In excessively hot weather infants, whether suffering from diarrhea or not, sometimes lapse into a state indistinguishable from that described as alimentary intoxication. The term "heat stroke" has been applied to this condition. There is little doubt that it is often the result of a desiccation of the body. The nervous symptoms presented by these infants are a combination of those observed in uremia and in shock. That the infants are virtually suffering from both of these conditions has already been shown.

To sum up: The entire clinical picture presented by infants who have lapsed into a toxic, shocklike condition following severe diarrhea may be explained on the basis of the water loss from the body, which is known to occur. That factors other than water loss are operative cannot be denied, but it is unnecessary to assume the existence of other factors in order to explain the observed facts. If poisons are accountable for the symptoms, their origin, nature and mode of action has not yet been explained. The supposed toxic action of sugar and salt have been discussed. Efforts to produce the symptoms in animals by feeding or injection of intestinal contents or extracts of intestinal contents of these infants have failed.[30]

Mellanby[31] has suggested B-imidazolethylamine (histamin), a product of bacterial action on histidin, as a cause of toxic symptoms. This substance when given by mouth to animals causes diarrhea and vomiting and when injected intravenously gives rise to shocklike symptoms, but the condition of the blood after such injection is quite different from that observed in these infants. There is no desiccation and the protein content is low or normal. The same may be said of the action of proteoses, which have been suspected of passing unchanged through the gastro-intestinal wall into the circulation.

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28. Langstein-Meyer: Säuglingsernährung und Säuglingsstoffwechsel, Wiesbaden, 1914, p. 41.

29. Rietschel: Monatschr. f. Kinderh. **9**:39, 1911.

30. Czerny and Salge: Quoted by Langstein-Meyer, Säuglingsernährung und Säuglingsstoffwechsel, Wiesbaden, 1914, p. 296.

31. Mellanby: Quart. J. Med. **9**:164, 1915.

So far no mention has been made of the original cause of the diarrhea. A full discussion of this question would occupy more time than that allotted to this paper. Suffice it to say that whether the diarrhea is the result of an excess of fat or carbohydrate in the food, whether it is secondary to parenteral infections or itself of infectious origin, whether due to nervous influences or the injudicious administration of cathartics, the end result is the same. Once anhydremia has occurred, a "vicious circle" is established which still further results in lowering the functional capacity of the gastro-intestinal tract. Heubner,[32] in voicing his skepticism concerning Finkelstein's conception of a food poisoning as the cause of the symptoms, draws attention to the fact that the clinical picture of Asiatic cholera, a disease entirely unrelated to food disturbances, is identical with that observed in infants supposedly suffering from food intoxication. He suggests that the younger generation of pediatricians are probably not familiar with Asiatic cholera and, therefore, take no cognizance of this fact in theorizing about the cause of the symptoms.

If a negative water balance occurring as the result of diarrhea leads to a characteristic symptomatology, the same symptoms should also occur as the result of a negative water balance dependent on other causes. This we have found to be the case. Dr. Perkins and I made a number of observations on infants who presented symptoms indistinguishable from those following severe diarrhea. As a criterion of the degree of desiccation of the body fluids we determined the index of refraction of the blood serum. This determination is one which is easily carried out within a few minutes time and requires only one or two drops of serum. It has the advantage that it may be repeated at frequent intervals. The refractive index varies with the concentration of solids in solution. As the protein has much greater effect on the index than the other solid constituents of the serum, it is possible, as shown by Reiss,[10] to determine quite accurately the protein content of the serum by means of the refractometer. By the use of this method he found the protein content of the serum of normal infants during the first six months of life to average about 6 per cent. Toward the end of the first year it was often as high as 7 per cent. These figures have been confirmed by Salge[11] and by ourselves. The protein content of the serum normally varies somewhat from day to day in the same infant, but the variations are not great. With a drying out of the blood the protein concentration necessarily increases. Such we have invariably found to be the case in the serums of infants suffering from the intoxicationlike symptoms following severe diarrhea. We have observed an increase in the protein content of the serum of as great as 50 per cent. above the normal for the age. Applying the refractometric method, we were able to demonstrate a state of anhydremia in a number of conditions quite unrelated to diarrhea. For example, a microcephalic idiot 5 months old had taken only extremely small amounts of food or water for some days. This infant on admission to the hospital presented the typical symptoms of an intoxication with the sole exception of the diarrhea. The blood protein was 9.35 per cent. On the administration of a considerable amount of saline parenterally the protein content of the blood dropped to 6.6 per cent. At the same time, there was a disappearance of practically all of the symptoms of intoxication. This infant took very little of anything by mouth and two days later the blood protein had increased to 8.4 per cent. and toxic symptoms were again present. The administration of food by gavage resulted in vomiting and diarrhea, symptoms which had not been present previously. The child lost 400 gm. in weight during the succeeding twenty-four hours and the blood protein concentration rose to 9.5 per cent. The symptoms were those of an extreme degree of intoxication. Despite the parenteral administration of large amounts of saline, it was impossible to maintain a normal water content of the body. The protein concentration of the serum never again became lower than 8.2 per cent., and the symptoms remained present until death occurred. In this case the dehydration was originally brought about by an insufficient fluid intake. When food was given, diarrhea and vomiting occurred, just as in the case of Straub's dehydrated dogs. The vomiting and diarrhea in turn still further increased the dehydration.

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[32] Heubner: Lehrb. d. Kinderh.

We have observed a marked degree of anhydremia in infants suffering from pneumonia, from otitis media and from pyelitis. Some of these patients were vomiting and had been refusing part of their feedings. The toxic symptoms were especially marked in those patients showing considerable concentration of the blood.

The literature contains many references to the occurrence in newly-born infants of transitory fever, sometimes accompanied by toxic symptoms. The observations of Holt[33] and Crandall[34] on this condition has led to the view that the symptoms, in at least some instances, are the result of an insufficient intake of fluid. Recently much additional evidence in support of this hypothesis has been brought forward, notably by E. Müller[35] and by Rott.[36] The latter in a small series of cases demonstrated an increased desiccation of the body at the height of the fever.

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[33] Holt: Arch. Pediat. **12**:561, 1895.
[34] Crandall: Arch. Pediat. **16**:174, 1899.
[35] Müller: Berl. klin. Wchnschr. **47**:673, 1910.
[36] Rott: Ztschr. f. Kinderh. **1**:43, 1911.

It is thus seen that desiccation of the body occurs in a great variety of conditions, and that the symptoms are essentially the same, no matter what the original cause. Diarrhea is by far the most frequent etiologic factor, but I do not feel that sufficient evidence has yet been introduced to warrant the assumption implied in the use of the term "alimentary intoxication" or "food poisoning." In the light of our present knowledge, the term "anhydremia" is accurately descriptive of the underlying factor and seems a suitable one to apply to all of these conditions, irrespective of the original cause.

If an infant suffering from diarrhea is given food, especially an excess of carbohydrate or fat, the diarrhea becomes worse and consequently the degree of anhydremia tends to become greater. If food is given to an individual who is anhydremic, even though diarrhea is not present, it is likely to result in diarrhea as has been previously mentioned. Furthermore, it has been shown by Straub in his experiments on dogs that anhydremic animals die sooner when food is administered than if they are completely starved, the explanation being that the soluble metabolites accumulating in the blood still further increase its osmotic pressure and decrease the available water reserve. We have in these facts adequate explanation of Finkelstein's observations that the giving of food increased the symptoms of his infants suffering from "alimentär intoxikation."

If the symptoms of the condition we are discussing are the result of anhydremia, they should disappear when a sufficient amount of fluid has been introduced into the body. In the case of a moderate degree of anhydremia resulting from insufficient fluid intake, the symptoms usually disappear rapidly after the administration of fluid by mouth. In the case of postdiarrheal anhydremia, the results are less striking. In the first place it is usually impossible to administer a sufficient amount of water by mouth. The water deficit of these patients is approximately the same as the amount of weight lost, that is, it may be from 300 to 1,500 gm., even in young infants. On account of the fact that vomiting and diarrhea are still present and that there is an excessive loss of water by evaporation as the result of increased metabolism chiefly of protein, water loss is so great that it is difficult to give enough water by mouth to keep the infant in water balance, to say nothing of introducing in a short period of time the extra amount required to make up for the deficit. Physiologic sodium chlorid solution may be given subcutaneously and a small amount intravenously, but these methods are only too often insufficient to restore normal conditions in the blood and tissues. By far the most efficient means of introducing water into infants of this type is by way of the peritoneal cavity. This procedure has been used to some extent in English clinics, but its great value seems to have been little appreciated until Howland[37] made extensive use of it in his clinic. Since that time the method has become widely used and it has been the general experience that the intraperitoneal administration of large amounts of normal saline at frequent intervals is the most efficient therapeutic measure at present at our disposal. Inasmuch as these children have suffered a loss of mineral matter as well as of water and protein, there would seem to be a theoretical advantage in administering other salts in addition to sodium chlorid. Holt, Courtney and Fales,[5] on the basis of their metabolic studies, have recommended such a procedure. In our experience Ringer's solution is an excellent substitute for physiologic sodium chlorid solution. It is unnecessary to administer alkali to correct the acidosis unless this is of a severe grade, for when sufficient amounts of water are given the acidosis disappears, as the conditions which have led to its production are no longer present.

The loss of water from these infants has sometimes been so excessive that recovery is impossible, no matter what means are used. This it also has been found is the case in animals rendered anhydremic by various means. This is presumably on account of the destruction of body protein, which is known to occur. Lack of fluid intake rarely leads to such a severe degree of anhydremia that recovery is impossible unless at the same time there is an excessive loss of water from the body. Thus it has been demonstrated that animals subjected to complete food and water starvation may live for considerable periods of time providing there is no excessive loss of water by way of the gastro-intestinal tract or by evaporation. Sufficient water is produced in the metabolic processes to provide for the water balance. Any increased water loss from such animals results in the development of acute symptoms, ending in death.

Mention has already been made of the fact that many of the infants developing toxic symptoms following diarrhea are, to begin with, in extremely poor nutritional condition. The increased protein destruction during the period of anhydremia still further affects the nutrition so that although recovering from the effects of anhydremia the infants succumb as the result of the other condition.

In order to spare the protein destruction, the administration of carbohydrate is desirable. During the stage of acute symptoms glucose may to advantage be given intravenously, but always at such a rate and in such concentration that glycosuria does not occur. As glucose is completely metabolized, the water in which it is dissolved becomes entirely available. Glucose infusions, temporarily at least, increase the blood volume and this is an advantage. Glucose in isotonic solution has been given intraperitoneally with excellent results, but in a certain number of instances this procedure leads to quite marked abdominal distention.

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[37] Blackfan and Maxey: Am. J. Dis. Child. **15**:19 (Jan.) 1918.

So much for therapy based on the conception of the pathogenesis of the condition. Curative measures can accomplish something, preventive ones much more. With an understanding of the nature of the disturbance, the problem of prevention is simplified.

Fortunately, relatively few infants suffering from diarrhea develop the severe toxic symptoms which have been recounted; it is usually those who have suffered from repeated attacks and whose nutritional condition is, as a result, far below par. Infants who are already in a condition commonly referred to as marasmus are those likely to finally succumb to the intoxication of anhydremia. It is this chronic condition of malnutrition which will next be discussed.

Anyone who has frequented the wards of an infant's hospital is only too familiar with the picture of these wasted infants. The condition exists in all degrees of severity, and it is often difficult to state just when it begins. An artificially fed infant may begin to vomit occasionally, the stools may vary from the normal, there may be constipation or more frequently repeated attacks of diarrhea, the weight fluctuates and then usually declines. If the feedings are increased diarrhea results, if decreased loss of weight continues. In other instances an infant may be thriving until some parenteral infection occurs which becomes chronic, for example, pyelitis or bronchitis. The weight progressively declines. Other infants fed on very dilute milk or insufficient amounts of proprietary foods never do well and the weight decline begins almost at birth. Ultimately, in each instance, the infant wastes to a skin covered skeleton. The paper thin skin has a gray pallor, the hands and feet are cold, the pulse slow, small and weak and the temperature often below normal, although heat production as measured in the calorimeter is markedly higher per kilo of body per day than that of normal infants. The blood is thin, pale and has a low hemoglobin and red cell content. The white blood count is often moderately increased. The urine is essentially normal in amount and in character except for a somewhat higher ammonia coefficient. From the metabolic standpoint, the most outstanding features of the condition are an inability to utilize food and a negative nitrogen and mineral salt balance. The picture is that of advanced starvation but often it is a starvation in the midst of plenty.

Various names, other than marasmus, have been applied to the condition. It is known as "infantile atrophy," "dekomposition" or "athrepsia." The latter term, applied by Parrot, is, perhaps, most accurately descriptive of the condition and, therefore, the preferable one.

No anatomic basis for the symptoms of this condition has been found, and here, as in the case of the intoxication states already discussed, it is necessary to assume an alteration in the chemical and physiologic processes of the body. The fact that some of the symptoms of the two conditions are identical and that one often merges into the other would lead one to suspect the presence of some common underlying factor operative in both. It, therefore, seemed worth while to apply the same methods previously used in the study of anhydremic cases.

Dr. J. F. Perkins and I began the study with the investigation of the protein content of the serum by the refractometric method. Very soon we were struck by the fact that the concentration of the protein in the serum of these infants was usually lower than the average for normal infants of the same age. The fact that there was also a diminution in the red blood cells and hemoglobin suggested that either the blood was hydremic by dilution with water or else that a destruction of both serum protein and cells had occurred. If the blood were hydremic there should be an increased blood volume, if destruction had occurred, a decreased volume. In order to determine which of these conditions was present, we made use of the vital red method for blood volume estimation.

In studying seven approximately normal infants under 1 year of age, two of whom were undernourished but gaining well, we found the average blood volume to be 9.1 per cent. of the body weight. The extreme variations were from 8.0 to 10.8 per cent. of body weight. Applying the same method to eleven athreptic infants, the blood volume was found to average 8 per cent. of the body weight, the extreme variations being from 4.8 to 10.4 per cent. The higher values in general were observed in those infants who might be considered as convalescing from the condition.

It is questionable if relationship to body weight is the best method of expressing blood volume when comparisons are to be made of individuals in different nutritional condition. Adipose tissue being relatively nonvascular, a thin individual of the same length and musculature should have a relatvely larger blood volume in proportion to body weight than a fat individual. The bodies of the marasmic infants that we studied were obviously almost free from fat. If the absolute blood volume of these had not been changed during the period of wasting the relation of blood volume to body weight should have been distinctly higher than under normal conditions. The very fact that the infants studied had a lower blood volume both absolutely and in relation to the body weight indicates that a very considerable destruction of the blood must have occurred along with the breakdown of other parts of the body.

As a result of the decrease in blood volume one would expect that volume flow would also be diminished. This was found to be regularly the case. The volume flow was often less than one-fifth, occasionally less than one-tenth of the normal. During convalescence the volume flow invariably increased.

An additional factor leading to such poor circulation is the condition of the heart muscle. Electrocardiographic tracings made on the infants of this series by Dr. Hugh McCulloch[38] showed occasionally, but by no means regularly, alterations from the normal complexes. The most marked variations were a low amplitude of all waves, and P and T waves being frequently isoelectric, a lengthened P-R interval and broad Q R S complexes. These variations were seen to disappear during convalescence. Whether these functional alterations are to be attributed to organic changes in the heart muscle or merely to an insufficient circulation through the intrinsic cardiac vessels is problematical. The rapid and complete recovery speaks for the latter supposition.

The decreased blood volume of these infants results in constriction of the arterioles and this leads to a piling up of corpuscles in the capillary blood. A large number of determinations of hemoglobin and red blood cells on venous and capillary blood from these infants invariably showed this corpuscular concentration in the capillary blood,[17] the increase being not infrequently as great as 20 per cent. over the venous blood. This fact may explain the gray color of the skin.

Arteriolar constriction may be considered a compensatory mechanism to maintain blood pressure at its normal height. In the case of anhydremia we have seen that the constriction is usually sufficient to maintain blood pressure but here there is the added factor of increased blood viscosity. In the athreptic infants the viscosity of the blood is not increased, and consequently the blood pressure sometimes falls below normal limits.

Sufficient has been said to provide the explanation for such symptoms of athrepsia as are identical with those of anhydremia. In the light of these facts, it is also easy to understand why an infant with a blood volume already diminished by atrophy should, when that volume is still further decreased by even a moderate degree of desiccation, readily develop the severe toxic symptoms characteristic of anhydremia.

In uncomplicated cases of athrepsia there is no increase in the concentration of the body fluids and no bar to the free evaporation of water, fever consequently does not occur. There is no increase in the colloidal osmotic pressure of the blood, hence no diminution in the amount of urine secreted and no accumulation of urinary waste products in the body. Such acidosis as may occur is to be ascribed to causes other than the retention of acid products by the kidney. The acidosis is probably in part due to the diminished volume flow of the blood through the tissues and to a lesser extent to production of acetone bodies, the latter the result of partial starvation. Acidosis is, however, by no means a prominent feature of this condition.

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[38] McCulloch: Am. J Dis. Child. **20**: 1920. To be published.

We have no direct proof that the volume flow of the blood throughout the body is diminished to the same degree as in the extremities where it has been found possible to measure it. That some decrease of the blood to other parts of the body does occur, would seem likely, and it would not be unreasonable to suppose that such a diminution in the blood flow would seriously impair the functional activity of the gastro-intestinal tract, and interfere with the whole nutrition of the body. We know that following hemorrhage the nutrition suffers until the blood is restored; the same is apparently true in the case of athreptic infants, but in these infants there is, unfortunately, very little tendency to build up new blood. Transfusions have a temporary value only unless the underlying cause of body destruction is found and remedied.

So far we have discussed the effects of the breakdown of body tissues and but little has been said as to its cause. We know that simple starvation or a supply of food insufficient to cover the basal energy requirement of the body results in the destruction of the body itself in order to supply the fuel demands. The stored glycogen and fat are burned in preference to protein but when the fat and carbohydrate stores are exhausted a general consumption of protoplasm occurs as is evidenced by a markedly negative nitrogen and mineral salt balance. In a fair proportion of cases of athrepsia insufficient food intake is the obvious cause. Prolonged underfeeding either with natural or artificial food leads to the condition, and once it is fully developed the tolerance for food may be so low that it is impossible to give a sufficient amount to cover even the basal energy requirement.

It has been possible to duplicate exactly the condition of athrepsia in rabbits by prolonged underfeeding.[17] In such animals the blood volume decreased both absolutely and in proportion to the body weight and surface area. The volume flow of the blood decreased much more proportionately than the blood volume. The corpuscular count and volume diminished. When feeding was begun these animals maintained stationary weights for days even though given unlimited food. The blood volume was almost uniformly regained before any weight increase was observed. Following this restoration of blood volume and volume flow there was a tendency for the weight curve to start upward. The majority of the rabbits ultimately made a complete recovery, but in a few the normal volume of the blood was not regained, and all of these did badly; the weight curve remained stationary and ultimately fell; all of these animals died. These experiments serve to emphasize the importance of blood volume in relation to nutrition, and lead one to suspect that the "period of repair" observed in the case of infants convalescing from athrepsia is a period during which the restoration of blood volume is occurring. Once this has been accomplished improvement is likely to be rapid and steady. If the blood volume is not regained the prognosis is poor.

An insufficient intake of food by mouth is by no means the only cause of athrepsia. In many instances the food given an infant is sufficient in calories but is either incompletely digested and absorbed or else it is not completely utilized by the body tissues after absorption.

Practically every infant normal at birth and free from infection will thrive when fed from the beginning on a sufficient amount of breast milk, but when the same number of calories or even the same proportion of fat, carbohydrate and protein are fed in the form of cow's milk a certain number of infants fail to gain and ultimately lapse into a state of severe malnutrition. There seems to be something about cow's milk which renders it unsuitable for these infants but there has been little unanimity of opinion as to just why cow's milk is unsuitable. The teleological explanation that cow's milk is made for the calf and not for the baby hardly suffices without further qualification.

At one time it was believed that the protein of cow's milk was the cause of the trouble but the modern conception, at least of the German school, seems to be that protein can do no harm, an idea which has not gone unchallenged. There are chemical differences in the fat of human and of cow's milk sufficient to account for some but not all of the differences in behavior of the two kinds of milk in the infant's body. The carbohydrates of human and of cow's milk differ only in quantity, but cow's milk cannot be made equivalent to breast milk by merely adding the extra 2.5 per cent. of lactose. The mineral salts of human and of cow's milk are quite different in character and amount, and Finkelstein believes this to be an important factor. According to him the whey salts of cow's milk may injure the intestinal mucosa and interfere with its functional activity, by way of decreasing its normal secretions and also by permitting the passage of harmful substances into the circulation. With an injured mucous membrane conditions are favorable for abnormal bacterial activity in the intestine. The whey salts of cow's milk are in addition supposed to upset the normal mineral equilibrium of the body and lead to a loss of essential ash constituents.

In the attempt to demonstrate the harmfulness of the whey salts of cow's milk Meyer[39] performed his well known "whey exchange" experiments. He mixed the curds of cow's milk with the whey of breast milk and the curds of breast milk with the whey of cow's milk. Each of these mixtures were fed to infants convalescing from nutritional disturbances. On the basis of a limited number of experiments Meyer claimed to have shown that cow's milk curds in breast milk whey was well tolerated, whereas those infants fed on breast milk curds in cow's milk whey showed an increase in all the symptoms of a nutritional disturbance. He concluded from these experiments that cow's milk whey had a distinctly harmful influence. Such a definite, far reaching conclusion seems unjustified when we consider the differences in the caloric value of the two mixtures prepared by Meyer and also the different relationships between the organic constituents.

Within the past year Lichtenstein and Lindberg[40] repeated Meyer's experiments on a large number of infants and were unable to confirm his results or to substantiate his conclusions. They aptly state that the refutation of this theory amounts to "the removal of one of the cornerstones of Finkelstein's teaching structure."

There is a certain amount of good evidence that bacterial invasion of the upper intestine may occur in the case of infants suffering from nutritional disturbances. This has been demonstrated at necropsy by Moro[41] and others and by Bessau and Bossert[42] on living infants. This bacterial invasion may well be the factor in interefering with normal processes in digestion and absorption and hence with the actual amount of available food entering the circulation and brought to the body cells.

Abnormal bacterial growth in the upper intestine seems to be more frequent in infants fed on cow's milk but this is evidently not due to any greater bacterial content of the cow's milk as fed. Furthermore even apart from any bacterial factor, cow's milk often fails to satisfy the nutritional demands of certain infants.

There is one difference between breast milk and cow's milk which, it seems to me, has not been sufficiently emphasized, although it is mentioned in the literature. That is the high "buffer" value of cow's milk as compared with breast milk. By buffer value we mean a

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39. Meyer: Monatsh. f. Kinderh. **5**:361, 1906.
40. Lichtenstein and Lindberg: Jahrb. f. Kinderh. **89**:329, 1919.
41. Moro: Jahrb. f. Kinderh. **84**:1, 1916.
42. Bessau and Bossert: Jahrb. f. Kinderh. **89**:213, 269, 1919.

capacity to unite with relatively large amounts of acid or alkali without a great change in chemical reaction. If the same amount of hydrochloric acid is added to equal volumes of human milk and of cow's milk it is found that the acidity of the human milk expressed in terms of hydrogen ion concentration is far greater.

When milk enters the stomach of a normal infant gastric juice is secreted in such amount that the stomach contents ultimately reach a certain degree of acidity. This acidity expressed in terms of H-ion concentration averages about 1×10^{-5}, which is the optimum concentration for rennin action and is sufficient to markedly inhibit bacterial growth (Hahn [43]). The presence of acid on the gastric side of the pylorus initiates a reflex which allows for the passage of food into the duodenum. Here we know, from the work of Bayliss and Starling,[44] the acid acts on some substance in the mucous membrane which results in the production of the hormone "secretin," a substance capable of stimulating pancreatic and biliary secretion. Such is the normal course of events when the infant is fed on breast milk. Suppose, however, cow's milk instead of breast milk is fed. If the same amount of gastric juice is secreted, it is entirely insufficient to render the stomach contents acid to anywhere near the same optimum degree. To bring cow's milk to the optimum acidity of 1×10^{-5}, at least three times as much hydrochloric acid is required as in the case of human milk. (This may readily be demonstrated by titrating breast milk and cow's milk with diluted hydrochloric acid, using as an indicator neutral red which changes color at a hydrogen ion concentration of about 1×10^{-5}). We must, therefore, assume that the stomach secretes three times as much acid, or else that the optimum acidity is not reached. To secrete this extra amount is probably beyond the functional capacity of certain infants, yet if this amount is not secreted, bacterial inhibition and rennin action in the stomach occurs to only a slight degree. Without the passage of a sufficiently acid chyme into the duodenum, secretin formation and the hormone stimulation of the pancreatic and biliary secretion would necessarily be greatly diminished. In the light of these conditions, is it any wonder that certain infants fail to thrive on cow's milk which has been insufficiently diluted?

It is interesting to note that those foods which have been found empirically to be the best tolerated by athreptic infants are those which have a low buffer value or in which the buffer is already partly neutralized by acid. Breast milk, well diluted cow's milk with added carbohydrate, lactic acid milk and protein milk are examples.

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[43] Hahn: Am. J. Dis. Child. **7**:305, 1914.

[44] Bayliss and Starling: J. Physiol. **28**:325, 1902.

Some infants waste even when fed on considerable amounts of breast milk and when there are few gastro-intestinal symptoms. For some reason these infants are unable to make use of food. Congenital cardiac disease or chronic infections may be present, but occasionally no cause can be found, and we are compelled to make use of Czerny's term "abnormal constitution," to cloak our ignorance.

Athrepsia is essentially a condition of starvation dependent on any number of causes. But no matter what the cause, the end result is the same and that result is destruction of body tissue. In athrepsia, as the name implies, we have a clinical picture due to lack of nourishment. The obvious treatment is to supply food in such form as can be utilized by the body. The amount of food required is large for the basal energy requirement is high, and, in addition, much lost tissue must be replaced. Many of these infants fail to gain on less than 150 or 200 calories per kilo per day. The idea fostered by the German school that the condition is a result of food poisoning has no basis of fact and has resulted in much gross underfeeding of infants of this type. There is no good reason to believe that food, once it has passed the gastro-intestinal tract, is capable of harming these infants; diabetes, of course, being excluded. The feeding of an excess of indigestible food sets up an abnormal condition in the gastro-intestinal tract, so that less food is actually absorbed than when smaller amounts of more easily digested food is given.

Athreptic infants need calories; they also need protein, mineral salts, and the necessary accessory substances known as vitamins. Excessive amounts of protein are not required, certainly not more than 10 per cent. of the total caloric intake need be in the form of protein.

Fat is valuable chiefly for its vitamin content (fat soluble A). The digestive tract of these infants is, however, incapable of caring for excessive amounts of fat. Carbohydrates spare protein and are the most easily assimilated of all the foods. Carbohydrate must be relied upon to supply the greater part of the energy requirement of athreptic infants. It has been shown by Helmholz and Sauer [45] that the metabolic tolerance of these infants for sugar is exceedingly high. The problem is to give considerable amounts of carbohydrate without at the same time producing gastro-intestinal disturbance. Dextrin, because it is not readily fermented and on account of the fact that it has a high molecular weight and hence in solution exercises a relatively low osmotic pressure, is less likely to cause trouble in the gastro-intestinal tract than are some other sugars. Starch has some of the same characteristics as dextrin but is not quite so readily digested.

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45. Helmholz and Sauer: Proc. Am. Pediat. Soc. **31**:256, 1919.

The actual percentage of carbohydrate in the food given is relatively unimportant. The percentage of carbohydrate which can be tolerated by the gastro-intestinal tract is dependent on the form of mixture in which it is fed, as well as upon the type of sugar. Mixtures of lactic acid whole milk containing as much as 10 per cent. of added carbohydrate are often very well tolerated by these athreptic infants.

Carbohydrate can be given in other ways than by mouth; for example, glucose can be administered intravenously or intraperitoneally. We have repeatedly given small infants more than an ounce of glucose a day by the latter method.

Even though a sufficient number of calories and an abundance of protein is supplied to these infants, they cannot build up protoplasm without mineral matter. The milk given may or may not supply the ash requirement. There may, therefore, be a theoretic basis for the administration of an extra amount of mineral matter. The French have indeed claimed beneficial results from subcutaneous administration of diluted sea water.

The accessory food factors or vitamins which are recognized as essential in the nutrition of the infant are all contained in milk, a food which necessarily forms the basis of the diet of these infants. The vitamin content of milk is known to be sufficient for the needs of normal infants, but recently the question has been raised as to whether or not the vitamin content of cow's milk is sufficient for the requirements of certain athreptic infants. Vitamins, especially the water-soluble B, have been added to the diet and according to Eddy and Roper [46] and Daniels and Byfield,[47] with excellent effect.

Mention has been made of the fact that the blood volume of athreptic infants decreases along with atrophy of the rest of the body. The blood volume decrease in itself, leads to severe symptoms, and seriously interferes with the nutritional processes. The blood volume tends to become restored through the period of repair, and is generally restored before the restoration of other parts of the body. Anything that would shorten this period of restoration should favorably influence the nutrition. Repeated blood transfusions and the intravenous injection of colloidal solutions, such as gum acacia, result in an increase in blood volume and volume flow, and are therefore theoretically indicated. I have repeatedly seen apparently good results from the use of such measures.

In the condition of athrepsia as in anhydremia, the therapeutic indications are clear, but only too often difficult or impossible of fulfillment. We have in one a clinical picture due to lack of water, in the other lack of nourishment; when these two essentials can be supplied and retained, recovery is possible, but only if the conditions have not existed for such a length of time that the body has been irreparably injured.

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[46] Eddy and Roper: Am. J. Dis. Child. **14**:189 (Aug.) 1917.

[47] Daniels and Byfield: Am. J. Dis. Child. **18**:546 (Dec.) 1919.

This discussion has been concerned with a consideration of some of the alterations in the physiologic and chemical processes occurring in the infant's body and with the methods of restoration of normal processes. It is interesting to note that those therapeutic procedures which are theoretically indicated in the light of recent work, are for the greater part exactly those procedures which have best stood the test of time and clinical experience.

STUDIES ON THE HEART IN NUTRITIONAL DISTURBANCES IN INFANCY *

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Infants who are suffering from nutritional disturbances and show signs of athrepsia may present various manifestations of circulatory derangements. Electrocardiograms have been made from a group of athreptic infants admitted to the St. Louis Children's Hospital, and it is my purpose to direct attention to certain observations made in the study of these cases.

Infants with athrepsia are in a state of partial starvation because the food they receive, for one reason or another, is not sufficient to supply the needs of the body tissues. An insufficient intake by mouth, an inability to completely digest and absorb food, or an inability on the part of the body tissues to completely utilize the food ingested are phenomena that lead to the development of this condition. Anatomic changes that might explain the symptoms associated with the condition have not been found in the body tissues, and it seems necessary to assume some alteration in the chemical and physiological processes and reactions of the body. Marriott[1] recently described the circulatory changes that occur in athreptic infants and brought out explanations for the various phenomena that occur in these infants. Briefly, the changes he describes are a slow, small and weak pulse; a surface temperature much below normal; a low hemoglobin and red blood cell count; concentration of the protein contents of the blood serum much lower than normal. The blood volume is much decreased, both absolutely and in relation to the body weight; the volume flow is often one-fifth, occasionally one-tenth of the normal; there is a constriction of the arterioles leading to a piling up of corpuscles in the capillary blood. The arteriolar constriction may be considered a compensatory mechanism to maintain blood pressure at its normal height; but despite this the blood pressure may fall below normal. He states that the evidence indicates that there is an increased tissue destruction throughout the whole body; the stored glycogen and fat are burned in preference to protein but when the fat and carbohydrate stores are exhausted, a general consumption of protoplasm occurs as is evident by a marked negative nitrogen and mineral salt balance.

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[1] Marriott: Some Phases of the Pathology of Nutrition in Infancy, Harvey Lectures, Series 1919-1920, Am. J. Dis. Child. **20**:461 (Dec.) 1920.

These observations on infants have been substantiated by Utheim,[2] working in Marriott's laboratory. By prolonged underfeeding, the blood volume of rabbits was decreased both absolutely and in proportion to the body weight and surface area; the volume flow was decreased, and the corpuscular count and volume were also decreased.

Burge and Neill[3] studied the oxidative powers of various tissues in the bodies of animals before and after starvation by measuring the catalase content of those tissues. They consider that the catalase content of a tissue is directly proportional to the amount of oxidation in that tissue. The heart, which is not autolyzed during starvation, shows a normally high catalase content which is not decreased during starvation. While that of the fat and skeletal muscles which are autolyzed during starvation, is greatly decreased and at the end of periods of starvation these tissues have an exceedingly low catalase content.

Electrocardiograms from infants showing various nutritional states have been made previously by many observers. In those infants with a severe loss of water and body weight, the curves often have shown abnormal forms of the ventricular complexes. Noeggerath[4] studied the electrocardiograms made from infants that were prematurely born, or who were suffering from disturbances of nutrition or from infection. He observed many curves with abnormal ventricular complexes and also noticed that severely atrophic infants show a slowing of the pulse due to a sinus bradycardia and not to a disturbed cardiac mechanism. He concludes that the electrocardiogram is of no value in estimating the degree of function of the heart in such infants, nor is the method of value in determining the prognosis; that its usefulness is restricted to the demonstration and analysis of disturbances of cardiac mechanism.

Czerny[5] examined the hearts of athreptic infants by roentgenograms and found that the area of the heart shadow is much decreased in size. The condition exists independently of a loss in water content of the infant and it is most pronounced immediately preceding death. He is inclined to think that the heart is incompletely filled during systole, due partly to the decrease in total blood volume, but most likely to a disturbed action of the diaphragm.

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[2] Uthheim: Study of the Blood and Its Circulation in Normal Infants and Infants Suffering from Chronic Nutritional Disturbances, to be published in Am. J. Dis. Child.

[3] Burge and Neill: The Effect of Starvation on the Catalase of the Tissues, Am. J. Physiol. **43**:58, 1917.

[4] Noeggerath, C. T.: Elektrokardiogramme Schwächliche Säulinge, Ztschr. f. Kinderh. **6**:396, 1913.

[5] Czerny, Ad.: Zur Kenntnis der Zirkulationsstörungen bei Akuten Ernährungsstörungen der Säuglinge, Jahrb. f. Kinderh. **80**:601, 1914.

Fletcher and Hopkins[6] studied the relation of acids, particularly lactic acid, to the activity of amphibian muscle, and conclude that the presence of acid products depends on how favorable the conditions that exist in the muscle are for oxidative processes. When the oxygen supply is adequate, there is no accumulation of acid products, but when factors are present which diminish the oxygen supply, the acid is increased and can be removed only slowly and with difficulty. Their experiments show that lactic acid formed in muscle from various causes follows this rule and its disappearance is dependent on the oxygen supply.

Burridge[7] has shown that the rate of propagation of contraction in the frog's ventricle may be delayed by the addition of inorganic acids in sufficient strength to the fluid with which the heart was perfused. He states further that after treatment of the heart with a sufficient strength of acid to cause the heart to stop beating, by replacing such acid solution by Ringer's solution containing sodium bicarbonate, spontaneous beating will be resumed but with markedly delayed conduction of the impulse through the ventricles.

Mines[8] concludes from his experiments that certain changes in the electrocardiogram which result from increased frequency of the heart beat may be due to changes in the hydrogen ion concentration in some region of the muscle. He states that it is only when the hydrogen ion concentration is raised above a certain value that the effect will appear. After a long pause the hydrogen ion concentration is certainly lower than after a period of activity. Oxidative removal of lactic acid is a slow process and during the pauses between successive contractions of the heart, the removal is certainly not complete. A long pause will mean more complete removal.

The work of Fletcher and Hopkins, of Burridge and of Mines offers experimental proof for the observations made by Robinson[9] in this laboratory. He reports cases in which there were abnormalities in the form of the electrocardiogram due to faulty conduction of the cardiac impulse through the ventricles. This faulty conduction, he considers, depends on what has been termed "functional fatigue" rather than on anatomic lesions involving the intraventricular conducting system. He cites examples in which derangement of the ventricular

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6. Fletcher and Hopkins: Lactic Acid in Amphibian Muscle, J. Physiol. **35**: 247, 1907.

7. Burridge: Propagation of Contraction in the Frog's Heart, J. Physiol. **45**: 6, 1912.

8. Mines: On Dynamic Equilibrium in the Heart, J. Physiol. **46**:349, 1913.

9. Robinson: The Significance of Abnormalities in the Form of the Electrocardiogram, Arch. Int. Med. **24**:422 (Sept.) 1919.

conduction has resulted from lack of time for conduction recovery after a ventricular contraction. In one case distinct improvement in intraventricular conduction followed slowing of the heart rate when longer diastolic pauses were present. The rate of recovery of conduction was observed also in this case to become more rapid with improved circulatory efficiency. He concludes, in part, that "lesions causing an insufficient blood supply to the ventricles are responsible for the presence of acid metabolites, which accumulate whenever the oxygen supply to the muscle is inadequate."

CLINICAL OBSERVATIONS

A group of sixteen infants who showed moderate or severe degrees of athrepsia were studied. Electrocardiograms were made on admission to the hospital and at subsequent times when the evidence indicated a material change in the clinical condition. Curves that were made within a period of twelve hours preceding death were not included since it was felt that any change in the electrocardiogram at that time might be due to the fatal cardiac failure rather than to the condition we are studying. Below are the curves selected from two of the cases which indicate functional changes in the cardiac mechanism.

CASE 1 (Children's Hospital No. 14454).—The patient was admitted to the hospital, July 21, 1919, for an acute intestinal disorder. He has been a normal baby, except for improper feeding, up to about one week previous to admission, when vomiting and diarrhea set in. The baby responded quickly to hospital care and was discharged well one week later. He began vomiting and having diarrhea again at home and returned to the hospital August 4. He was suffering then from severe athrepsia and anhydremia. Electrocardiogram 2760 was made shortly after his admission. Again he improved and was doing well when he developed ileocolitis and pyelitis. Electrocardiogram 2827 was made during this period. His lower resistance and nutrition were not sufficient to withstand the infection and he died September 24.

Electrocardiogram 2760 (Fig. 1), made August 17, shows no evidence of abnormal muscle preponderance. Q R S time is 0.080 second, not abnormal. The complex is normal in form, except that the waves are low in amplitude. This is particularly true in Lead I. The P wave is not present in Lead I and III; it is low in Lead II. The T wave is not present in Lead I and III; it is abnormal in form in Lead II. Ventricular rate 95.7 per minute. P R time, 0.200 second, is a distinct delay in an infant.

Electrocardiogram 2827 (Fig. 2), made September 4, shows distinct improvement in the cardiac condition as compared with Electrocardiogram 2760. The Q R S times is 0.080 second, but the amplitude of the waves is much increased and now seems normal. The T waves are well formed in all leads, the change being particularly noticeable in Lead I. The P waves likewise are easily made out in all leads. Ventricular rate 103.8 per minute. P R time, 0.160, a faster time than Electrocardiogram 2760.

Interpretation: The decrease in the time for auriculoventricular conduction, the faster heart rate and the improvement in the form of the Q R S, and T and P complexes, coincident with the decrease in the signs of athrepsia, would indicate an improvement in the function of the heart.

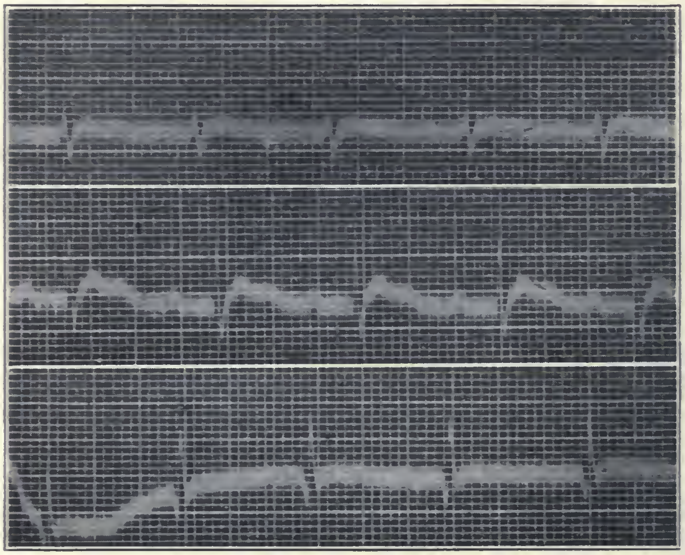

Fig. 1.—The Q R S complex is normal in form but the waves are low in amplitude. The P R time is 0.200 second, being slightly delayed. Ventricular rate, 95.7 per minute.

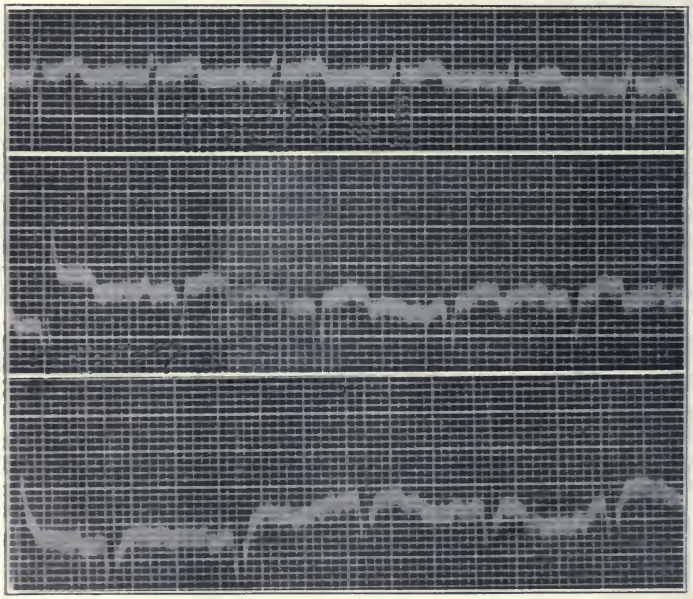

Fig. 2.—The amplitude of the Q R S complex is much increased. Ventricular rate, 103.8 per minute. The P R time is 0.160 second, the conduction time being much faster.

Case 2 (Children's Hospital No. 15063 and 15248).—Patient was admitted to the hospital, Jan. 22, 1920, suffering from marked degrees of athrepsia, anhydremia and acidosis. The findings in the study of the circulation were in accord with those described by Marriott. It is not shown how long she had been ill or what the previous feedings had been. She was discharged from the hospital in fair condition February 9. Electrocardiogram 3457 was made the day after her admission when her condition was at its worst. She was readmitted March 5 because of a return of her previous nutritional disturbance. Electrocardiogram 3711 was made at this time. Shortly after this admission she developed an acute otitis media which was followed by an erysipelas and she died.

Electrocardiogram 3457 (Fig. 3), made January 23, shows no evidence of abnormal muscle preponderance. The Q R S time is 0.060 second, not abnormal. The complexes are abnormal in form, particularly in Leads II and III. In Lead II the down stroke of the R wave is notched and in Lead III it is broadened out. Further, the waves are low in amplitude. The T waves are absent in all three leads. Ventricular rate, 150 per minute. The P R time is 0.160, an abnormal delay in an infant with such a ventricular rate.

Electrocardiogram 3711 (Fig. 4) was made March 7. As in Case 1 these curves show distinct improvement in the cardiac function. Q R S time is not shortened nor is the form changed, but the amplitude is much greater. The T waves are well formed though R T time, which is 0.240 second, seems much delayed. Ventricular rate, 138 per minute. The P R time is 0.120 second, a distinct improvement in the auriculoventricular conduction.

Interpretation: This curve was made at the time when the degree of athrepsia was not so marked and the patient seemed to be improving. It is probable that there was some improvement in the heart function.

In explanation of the alterations in the electrocardiogram reported by Robinson,[9] he states that sclerosis of the coronary vessels furnishes the condition for the increased production of acid metabolites and it also tends to delay their removal. Myocardial lesions, such as fibrosis would, perhaps, also tend to produce these effects by lessening the efficiency of the blood supply to the cardiac tissue. In athreptic infants the heart muscle and coronary vessels on examination have not shown any recognizable anatomic fibrosis or sclerosis. But the marked decrease in the blood volume and delay in blood flow with low protein content would certainly result in a deficient supply of oxygen to the body tissues, with a resulting increase in hydrogen ion concentration. These changes would furnish the conditions under which alterations in the cardiac mechanism might occur. Alterations have been found as shown in the examinations made by previous observers and in the two cases reported above. The alterations in these two cases are not extensive but they are distinct enough to show that a profound influence has been exerted on the heart. In spite of the protective measures that have been set up to spare the heart, they have broken down. There has been a delay in impulse conduction from auricles to ventricles and when the nutrition of the body improved this abnormal delay disappeared and the impulses passed freely from auricles to ventricles. Coincident with this the form of the T waves was much improved and the amplitude of the Q R S complex was increased.

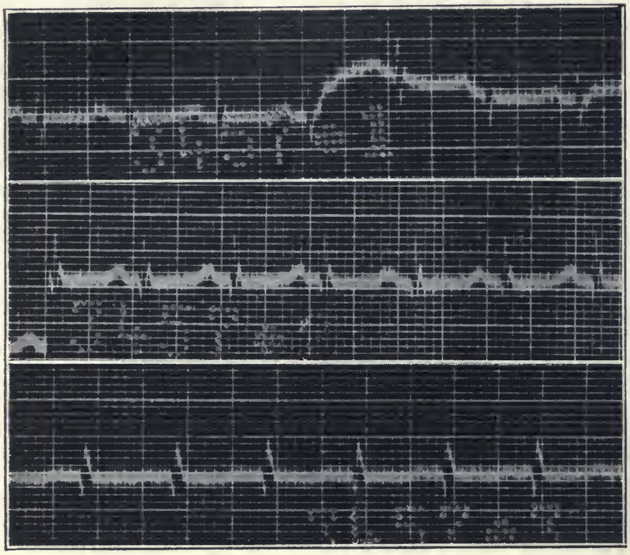

Fig. 3.—The Q R S waves are low in amplitude. Ventricular rate, 150.0 per minute. The P R time is 0.160 second.

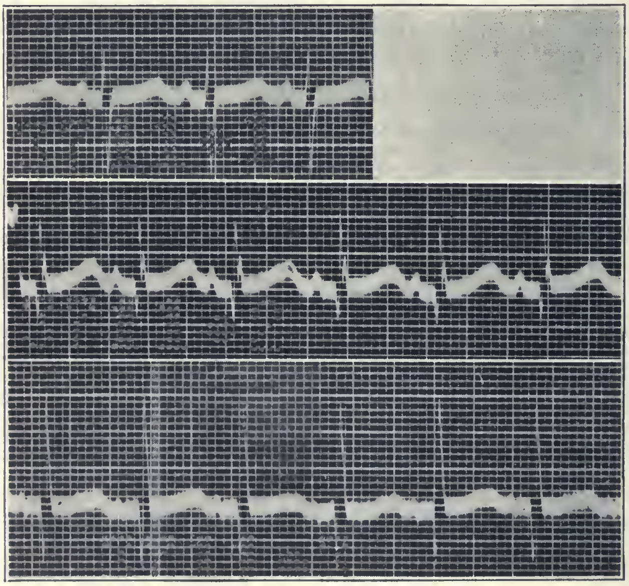

Fig. 4.—The amplitude of the Q R S waves are much increased. Ventricular rate, 138 per minute. The P R time is 0.120 second, being much faster than in Figure 3.

The changes described occurred in infants who were markedly athreptic, as evidenced by the other examinations on the circulation, but other infants suffering from athrepsia of just as severe a type have failed to give evidence of any disturbance in the electrocardiogram. Nor does the length of time that the nutritional disturbance has existed seem to be a factor in the production of functional changes in the heart. It is not to be expected that these changes would occur constantly for we must consider that several important factors are present in athreptic infants which delay the failure of circulation in the heart itself. The observations on volume flow, total volume and protein content of the blood have been made on the peripheral circulation of the body surface and especially in the extremities. It is both conceivable and probable that these same changes make themselves felt in the internal organs of the body, though possibly not to the same extent.

Phenomena that occur in one area of the circulation need not occur to the same degree or of the same kind in all the circulatory areas. In a pathologic state in which the circulation is altered to such an extent as in these athreptic infants, it is hardly conceivable that the internal organs can escape wholly some alteration in their circulation; truly, in mild cases no change may occur, but in the moderate and severe cases the profound changes observed in the surface area must spread to the deeper structures. Furthermore, it is probable that nature makes every attempt to provide primarily for the vital structures, the heart, brain and internal organs, and will endeavor to protect those structures from damage as long as possible. If the volume of blood is diminished, if the oxygen content is low, the blood will be diverted as much as possible by surface vasoconstriction into the circulation of those organs whose functional activity is essential to life. By withdrawing fluid from the rest of the body tissues, more fluid may be made available for the heart and other internal organs. If sufficient food for body needs is not received the glycogen and fat in the body tissue is used up and finally the tissue protein. The organs which are most essential for life, such as the heart and central nervous system, are preserved as long as possible, while organs which are relatively nonessential, waste away. It is probable even then that the heart is one of the last structures in the body to feel the effect of tissue destruction, one of the last structures in which the oxygen supply is diminished.

The hearts of infants suffering from athrepsia may be further protected by the decrease in heart rate so commonly observed. The more activity in the heart muscle, the more rapid the rate and the greater the need for oxygen. In experimental study it is found that when the surface areas become depleted of fluids and the blood vessels constricted to prevent further loss of heat, the animal becomes quiet and thus prevents muscular activity in those areas involved. The same phenomena occur in the heart. Functional fatigue appears to prevail if the oxygen supply is diminished and subsequently the cardiac mechanism is deranged. A slow heart rate acts as a compensatory mechanism to protect the heart muscle.

In making electrocardiograms from athreptic infants, we have found in most instances that the body resistance is very high and for this reason it is difficult to obtain satisfactory curves. The skin surface is dry and attempts to produce erythema and a moist skin with a high conductivity by rubbing with hot salt solution before applying the electrodes, is almost uniformly unsuccessful. It is common to find the body resistance as high as from 2,000 to 3,000 ohms, often higher. During convalescence in the favorable cases, coincident with the improvement in the circulatory conditions the body resistance is again lowered and the electrocardiogram may be obtained with the same ease as in a normal infant. Due to the withdrawal of fluid to other parts of the body the water content of the subcutaneous tissues is so much reduced that the electrical conductivity is lowered.

In some incompleted experiments we have attempted to produce alterations in the cardiac mechanism and in the form of the ventricular complex of animals. Up to the present time we have not succeeded in doing so.

We have no evidence that the alteration in the cardiac mechanism is dependent on structural change in the conducting tissue or the heart muscle. We think they are functional in nature resulting from an insufficient circulation of oxygen through the coronary vessels. Czerny's observation that the area of the heart shadow is decreased in size is probably due to incomplete filling of the heart chambers and coronary vessels.

CONCLUSIONS

1. Electrocardiograms were made from a group of sixteen athreptic infants, and in the case of two of these infants, alterations of cardiac mechanism were observed. The alterations consisted of a delay in auriculoventricular conduction, and changes in the form of the Q R S complex.

2. As an explanation of these disturbances we offer a suggestion that they are the result of alterations in the blood and body tissues in these infants suffering from nutritional disorders. It is probable that the changes which have taken place in the blood result in a deficient supply of oxygen to the heart, with incomplete or delayed removal of metabolic products (acid metabolites) from the cardiac tissue.

3. When improvement takes place in these athreptic infants the alterations in cardiac mechanism disappear. Measures adopted to relieve the nutritional disturbance seem to be the rational treatment for the cardiac condition as well.

4. We have not observed any phenomena indicating heart failure in these infants.

INFANTILE SPINAL PROGRESSIVE MUSCULAR ATROPHY (WERDNIG-HOFFMANN)

REPORT OF A CASE WITH NECROPSY FINDINGS *

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MINNEAPOLIS

In 1891, Werdnig,[1] a neurologist of Graz, gave the history, with necropsy findings, of a peculiar disease, which he termed early infantile progressive spinal muscular atrophy. This is his description:

> In a family without neuropathic taint, two or more children, who had been well up to that time, become sick about the tenth month of life, without fever, convulsions or other signs of infection. The disease begins very gradually, in that they cannot use their legs as well as formerly, the children never learn to walk and cannot stand without help. There is atrophy and paralysis of the muscles of the back and pelvic girdle (marked in the gluteal muscles), but especially in the quadriceps. The disease, in a chronic, progressive, centrifugal and symmetrical course, involves the shoulder girdle, neck and throat muscles, later the muscles of the thigh and arm, then the leg and forearm and last the muscles of the hands and feet. There is atrophy of the muscles en masse; there is no hypertrophy or pseudohypertrophy. Bulbar symptoms, fibrillary twitchings and secondary contractures may be present. There is marked flaccid paralysis with complete loss of the tendon reflexes and a partial loss of the skin reflexes, sitting up is very difficult or impossible. There is lordosis of the lumbar spine. There is no pain or tenderness anywhere, nor objective disturbance of sensation. Sphincters are normal. Mental development is good. There is extreme atrophy of the muscles, but not of the subcutaneous fat. There is involvement of the muscles of respiration and the disease runs a quick fatal course; in the mildest cases, within several years. The pathologic findings are primary symmetrical disease of the spinal cord, consisting of atrophy of the anterior horn cells, without evidence of any inflammatory process; a marked degeneration of anterior nerve roots; secondary simple atrophy of the muscles with more or less marked increase of nuclei; in places, degenerative atrophy and lipomatosis of the muscles.

These observations were confirmed by Hoffmann,[2] of Heidelberg, in 1893. Since that time, about fifteen typical cases have been reported, with only a few necropsy reports.

The English neurologists, especially Beevor[3] and Batten,[4] have contributed largely to our knowledge of this disease. In this country

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* From the Department of Pediatrics, University of Minnesota Medical School.

* Read before the Section on Diseases of Children at the Seventy-First Annual Session of the American Medical Association, New Orleans, April, 1920.

[1] Werdnig: Arch. f. Psychiat. **22**:706, 1891.

[2] Hoffmann: Deutsch. Ztschr. f. Nervenh. **3**:427, 1893.

[3] Beevor: Brain **25**:85, 1902.

[4] Batten: Brain **33**:433, 1910.

the only report on record is that of Bliss,[5] of St. Louis, who reports three cases in one family, but no necropsies were made.

In 1900, Oppenheim[6] described a new syndrome, which has been given various names, including amyotonia congenita and Oppenheim's disease, but the best term seems to be amyotonia congenita (Oppenheim). He described it as: "congenital, but not hereditary nor familial; present in full bloom at birth, consisting of a hypotonia of most of the muscles of the body, with absence of tendon reflexes and no reaction of degeneration, and a tendency to progressive improvement."

The pathologic anatomy was described as being primarily in the muscles, though Oppenheim did not exclude a secondary degeneration of the anterior horn cells.

Spiller,[7] of Philadelphia, was the first to report a necropsy of a typical case of this condition, and he found no spinal cord involvement. Councilmann and Dunn[8] and Leriboullet and Baudouin[9] report the same necropsy findings, but practically all the other reported necropsies of both the Werdnig-Hoffmann and Oppenheim types show the same spinal cord involvement originally reported by Werdnig.

Marburg,[10] of Vienna, gives the following differential diagnosis:

Amyotonia Congenita	Werdnig-Hoffmann
1. Congenital.	1. Acquired in early life.
2. Usually single, rarely familial.	2. Usually familial.
3. Generalized hypotonia.	3. Localized atrophies, beginning in the pelvic region and spreading.
4. Atrophy masked, not grossly apparent.	4. Atrophy easily recognized and apparent.
5. Tendon reflexes absent.	5. Proportional to the atrophies.
6. Stimulated by electricity or the hypotonic reaction given. (Farad. O., Galv. plus.)	6. Reaction of degeneration.
7. Course with improvement.	7. Progressively worse, a mere skeleton at 4 to 5 years.

However, the fact that the pathologic findings in muscle and spinal cord are the same in both types of cases, and the further fact that there are all shades of gradation between the typical Oppenheim and Werdnig-Hoffmann types, leaves it open to doubt whether they are not extreme types of the same disease.

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[5] Bliss: J. Nerv. & Ment. Dis. **44**:108, 1916.

[6] Oppenheim: Monatschr. f. Psychiat. u. Neurol. **8**:232, 1900.

[7] Spiller: Univ. Penn. Med. Bull. **17**:342, 1904.

[8] Councilmann and Dunn: Am. J. Dis. Child. **2**:354 (March) 1911.

[9] Leriboullet and Baudouin: Bull. et mém. Soc. méd. d. hô. de Par. **26**:1162, 1909.

[10] Marburg, quoted by Spiller: Arbeit. a. d. Neurol. Instit. Wien. **19**: 1912.

Collier and Wilson[11] are very firm in their conviction that they are two distinct entities and most other writers on the subject are inclined to agree with them.

Rothmann,[12] however, considers the two diseases identical. After an exhaustive consideration of the whole question, he comes to the following conclusions:

> 1. The disease picture of amyotonia rests, at least in the majority of cases, anatomically on a degeneration of the anterior horn cells, which may lead even to a complete disappearance of these elements.
> 2. Between amyotonia and Werdnig-Hoffmann disease we can have, according to our present material, all gradations with identical anatomic findings, so that we can draw no sharp distinction between the two disease groups.
> 3. From the whole group of early infantile spinal progressive muscular atrophy the congenital cases can be separated. Further, we can differentiate as amyotonia those cases which have come to a standstill and have a possibility of improvement, from spinal atrophy which becomes progressively worse and ends fatally.
> 4. We can have gradations between amyotonia congenita with involvement of the lower brain nerve roots and the Moebius "Kernschwund" with accompanying involvement of the cord.

At the International Congress of Medicine in London,[13] 1913, in a discussion of the relation of the myopathies, Batten and Spiller inclined to the same conclusion as Rothmann.

Careful survey of the literature shows that there are all clinical gradations between the two diseases and no definite pathologic distinction. All the cases of Werdnig-Hoffmann type and all but three cases[7, 8, 9] of the Oppenheim type show atrophy and disappearance of the anterior horn cells. The pathologic changes in the muscles are identical in the two diseases.

No sharp differentiation can be made between amyotonia congenita and the Werdnig-Hoffmann type on the ground that the former is congenital and the latter acquired in early life. Reference to the accompanying table (Cases 7, 8, 9, 16, 17, 22, 28 and 29) will show eight cases which were typically of the Oppenheim type, except that the disease was not present at birth. Neither can a definite distinction be made on the ground that the Werdnig-Hoffmann type is familial and that the Oppenheim type occurs singly. The table shows ten cases (Cases 14, 18, 20, 21, 34, 35, 39, 40, 41 and 42) in which otherwise typical Oppenheim cases are familial.

The points given by Marburg[10] in the differential diagnosis, relating to the extent of the atrophy, the condition of the reflexes and the electrical reactions, are so inadequately reported in the literature that they offer no basis for differentiation. The point that amyotonia tends toward improvement, while the Werdnig-Hoffmann type becomes progressively worse, offers no clear distinction. Reuben,[14] in a very complete report of 136 more or less typical cases of amyotonia, says of the course and prognosis:

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[11] Collier and Wilson: Brain **31**:1, 1908.

[12] Rothmann: Monatschr. f. Psychiat. u. Neurol. **25**:161, 1909.

[13] Batten and Spiller: Tr. Internat. Congr. Med., Sec. 11, Neuropath., pp. 2-125.

> In a great majority of the congenital cases the progress is one of slow but gradual improvement; however, in not a single case was there complete recovery; . . . in a small minority (thirteen cases) there was no improvement noted at any time; in these cases there was progressive deterioration up to death. In some of the cases in which there was progressive improvement there were noted long periods in which the condition was stationary. . . . The prognosis as to recovery is absolutely bad; there is no record of complete recovery in a single case. Of eighty-four in which the final outcome is stated, forty-five are known to have died.

The two cases in one family, reported by Bibergeil,[15] deserve special consideration. His second case is undoubtedly a typical case of Oppenheim's disease, except that it probably started late. His first case tended more toward the Werdnig-Hoffmann type; it was familial, had fibrillary twitchings, there was muscle atrophy, involvement of the facial and of the hypoglossal nerves, and differing degrees of hypotonia on both sides of the body. Against the diagnosis of the Werdnig-Hoffmann type is the tendency to improvement and absence of reactions of degeneration.

REPORT OF CASE

In connection with this controversy, a report of our case is of interest. The family history is very important and is given in full.

Father and mother are living and well, no history of syphilis, no miscarriages. The first child (male), aged 8, is in very good health. The second (female) died at 3 months. The mother had felt very weak fetal movements up to three weeks before birth, but they ceased altogether after that. The mother had remarked at the time that she "wondered what was wrong because the child did not move." The mother did not have the care of the child until it was 2 weeks old, but at that time she noticed that it did not move its legs and arms, but could move its toes and fingers and that it had difficulty in nursing and swallowing. The condition was so marked that a physician was consulted. The child seemed to improve in that it was able to bend its knees slightly which it had not done previously. At 3 months of age the baby "took cold" and died in three days, probably from bronchopneumonia. The mother considered the child better just before death than at 2 weeks.

The third child (Borghild) is the subject of our report. A fourth child (male) has since been born, is now 1 year old and normal in every way, both physically and mentally.

Three first cousins of the mother living in Norway, present an interesting history. One did not walk until 3 years of age, but is now well and strong; a second had some condition which started when she was 1 year of age. She did not walk very well, "limped on both feet," fell down very suddenly without warning, but without loss of consciousness. These falls would occur two or three times a day, and she was not able to walk more than one or two blocks at a time. She had something resembling contractures of the hands, is now an invalid and in bed most of the time. A third had exactly the same condition, but not so severely, still falls down occasionally, but is able to be up and about; she also holds her hands in a peculiar fashion. These two girls are now about 30 years of age. This history of the cousins was obtained from the mother, who went to school with the girls for a number of years.

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[14] Reuben: Arch. Int. Med. **20**:657 (Nov.) 1917.

[15] Bibergeil: Ztschr. f. d. Ges. Neurol. u. Psych. **22**:411, 1914.

Borghild J., the subject of this report, was a full term infant, breast-fed up to the fourth month, when allaitment mixté was instituted. The mother felt fetal movements all through the latter half of pregnancy. The child appeared normal from birth up to the age of 6 weeks, moved legs and arms and sucked fingers, and when lying prone tried to raise its head. At 6 weeks, the baby was vaccinated against smallpox, but the vaccination was unsuccessful, no scar remaining. At this time, the mother noticed that the child gradually grew weaker in its movements, especially of the hips; this gradually grew worse until death, the legs hanging limp when the child was held up. The arms were also involved, but the baby could lift a spoon to its mouth up to the last three weeks of life, and would try to grasp at a ball suspended over the crib almost up to the time of death. At 4½ months, with slight help (one finger supporting the chin) could hold up head, but at the fifth month this had become impossible. The mother first noticed difficulty in breathing at 4 months, the child would seem about to choke from the amount of mucus in the throat. At the same time it began to have difficulty in nursing, seemingly on account of the mucus and would gasp for breath. The baby had always had a weak voice from the first few days of life, this gradually grew weaker until it was reduced to a soft wail.

The baby was brought to one of us (E. J. H.) at the age of 5 months.

Physical Examination.—Weight, 6,200 gm., underdeveloped, undernourished, fontanel rather wide open, no craniotabes, musculature over entire body very flabby, almost doughy in feeling, skin pale. There was moderate dyspnea, with expansion of the alae nasi at each inspiration. There was extreme deformity of the chest, a modified Harrison's groove, the upper half of the chest being extremely narrow and the lower half, below the attachment of the diaphragm, flaring markedly. The chest was rather tympanitic and no abnormal dulness was noticed. The heart tones were clear. Abdomen, rather large and dependent, the liver palpable 3 cm. below the costal margin; spleen not palpable. Palmar and plantar surfaces clear. Knee jerks absent. Because of the difficult respiration and the deformity of the chest the possibility of some mediastinal condition was suspected and a roentgenogram of the chest was made. Shortly afterward, while being nursed, the baby went into collapse and seemed about to die. However, it revived after fifteen or twenty minutes, was taken home and a trained nurse was installed for several days.

This nurse was able to confirm many points of the mother's story; she reported in addition peculiar wavelike contractions of the trunk muscles, starting at the pectorals and spreading downward over the abdomen. The nurse described it as resembling the reverse peristaltic wave of pylorospasm, only more pronounced. The temperature was normal, but the child would have frequent attacks of slight collapse.

The collapse in my office seriously interfered with a further complete examination. Owing to the parents' objections, the electrical reactions could not be taken, nor a blood examination made. The child was seen four or five times during the following month, but no change in the condition was noted, except that the mother noticed adductions of the fingers of both hands, somewhat resembling tetany, though the muscles of the hands were not rigid. The child seemed mentally normal up to death.

The child died suddenly at the age of 6 months.

NECROPSY REPORT

External Appearances. — Body is 70 cm. long and fairly well nourished. There is a marked abnormality of the chest, both lateral surfaces being concave. There is a slight concavity in the anterior median line of the thorax, but not nearly so marked as the depression of the lateral surfaces. The inferior border of the thorax is outstanding, due to the depression of the other parts of the chest. The anterior fontanel measures 4 cm. transversely and 5 cm. anteroposteriorly. Other fontanels are closed. Circumference of head, 44.5 cm. Muscles are atrophic, those on the backs of the thighs being especially shrunken. Body has been embalmed. Slight lividity is present. No edema, cyanosis or jaundice. Pupils are 4 mm. in diameter and equal.

Peritoneal Cavity.—Embalming fluid is found in peritoneal cavity. There are no peritoneal adhesions. Marked atrophy of pectoral muscles. Mesenteric lymph nodes are prominent. Diaphragm extends to fourth rib on right side, to fifth rib on left side. Appendix shows no gross lesions.

Thymus.—Greatly enlarged, extending to the diaphragm on the right side of the median line and to 1 cm. of the diaphragm on the left side. It is distinctly lobulated and weighs 29.5 gm.

Pleural Cavities.—No fluid and no adhesions.

Pericardial Cavity.—Contains no excess fluid and no adhesions.

Heart.—Normal size. Chambers are not dilated. Valves, endocardium, and musculature show no lesions. Root of aorta shows no lesions.

Lungs.—Markedly collapsed. Crepitation is greatly reduced, especially in anterior and upper portions of lungs. No nodules are palpable. Cut surfaces show very little air. No pus. No excess of fluid.

Spleen.—Weighs 25 gm. Capsule is smooth and clear. Cut surfaces show prominent lymphoid follicles.

Liver.—Weighs 230 gm. Capsule is smooth and clear. Cut surfaces show no special markings. Gallbladder and ducts show no lesions.

Gastro-Intestinal Tract.—No gross evidence of disease.

Pancreas.—No lesions; lobules are distinct.

Suprarenals.—Greatly reduced in size, the right weighing 1.5 gm., the left 1.8 gm. The cut surfaces show no changes, except decreased thickness of the layers.

Kidneys. — Left weighs 20 gm.; right weighs 21 gm. External surfaces smooth. Cut surfaces show no special markings. Pelves are clear.

Bladder and Genital Organs.—No pathologic conditions found.

Aorta.—No gross lesions.

Lymph Nodes.—Fairly prominent throughout body, but not larger than is usual at this age.

Thyroid.—Weighs 3.6 gm.

Head.—No lesions found in the soft tissues of the scalp. Temporal muscles are atrophic. Meninges of brain show no evidence of disease. Sinuses of dura are clear. The cerebral convolutions show no evidence of atrophy. The brain is cut in coronal sections; no gross evidence of disease found. Portions reserved for microscopic examination.

TYPICAL AND ATYPICAL CASES OF WERDNIG-HOFFMANN TYPE

Case	Author	Necropsy	Age When First Seen	Onset	Diagnosis Reported	Course	Familial	Outcome
1	Werdnig[1]..........	Cord involvement	3 yrs.	10 mos.	W-H.*	Worse	Les	D. 5 yrs.
2	Werdnig[18]..........	Cord involvement	15 mos.	10 mos.	W-H.	Worse	Yes	D. 6 yrs.
3	Hoffmann[2].........	Cord involvement	4 yrs.	10 mos.	W-H.	Worse	Yes	D. 5 yrs.
4	Hoffmann[2].........	No necropsy	2¾ yrs.	10 mos.	W-H.	Worse	Yes	L. 3½ yrs.
5	Hoffmann[2].........	No necropsy	....	6-12 mos.	W-H.	Worse	Yes	D. 1½ yrs.
6	Hoffmann[2].........	No necropsy	9 mos.	5 mos.	W-H.	Worse	Yes	D. 15 mos.
7	Wimmer[19]..........	No necropsy	16 mos.	9 mos.	W-H.	Worse	No	Unknown
8	Haberman[20]........	Cord involvement	18 mos.	5 mos.(?)	O.	Worse	No	Died
9	Hoffmann[21]........	Cord involvement	1 yr.	7 mos.	W-H.	Worse	Yes	D. 3 yrs.
10	Hoffmann[21]........	No necropsy	9 mos.	9 mos.(?)	W-H.	Worse	Yes	?
11	Sorgente[22]..........	No necropsy	27 days	Birth	O.	Worse	Yes	D. 30 days
12	Sorgente[22]..........	No necropsy	5 days	Birth	O.	Worse	Yes	D. 20 days
13	Beevor[3]............	Cord involvement*	5 wks.	Birth	O.	Worse	Yes	D. 8 wks.
14	Collier and Wilson[11]	No necropsy	5 yrs.	Birth	O.	Better	Yes	D. 3 yrs.
15	De Villa[23]...........	No necropsy	3 yrs.	Birth	O.	Better	Yes	
16	Skoog[24]............	No necropsy	22 mos.	14 mos.	O.	Better	No	L. 22 mos.
17	Ritter[25]............	Cord involvement	15 mos.	5 mos.	W-H.	Worse	No	D. 16 mos.
18	Porter[26]............	No necropsy	3 yrs.	Birth	O.	Better	Yes	?
19	Batten[4]............	Cord involvement	4 wks.	Birth	W-H.	Worse	No	D. 4½ wks.
20	Batten[4]............	Cord involvement	5 wks.	Birth	W-H.	Worse	Les	D. 8 wks.
21	Batten[4]............	No necropsy	4 mos.	Birth	W-H.	Worse	Yes	Died
22	Batten[4]............	No necropsy	6 mos.	4 mos.	W-H.	Worse	No	Died
23	Batten[4]............	Cord involvement	8 mos.	Birth	W-H.	Worse	No	Died
24	Batten[4]............	Cord involvement	3½ yrs.	Birth	W-H.	Worse	No	D. 4 yrs.
25	Collier and Holmes[27]	Cord involvement	5 yrs.	Birth	O	Better	No	D. 7 yrs.
26	Collier and Holmes[27]	No necropsy	3½ yrs.	Birth	O	Worse	No	Died
27	Boudouin[28]........	Cord involvement	4 mos.	Birth	O.	Worse	No	D. 5 mos.
28	Marburg[10]..........	Cord involvement	3 mos.	6 wks.	O.	Worse	No	Died
29	Thomson and Bruce[29]	Cord involvement	?	1 yr.	O.	Worse	No	D. 8 yrs.
30	Griffith and Spiller[30]	Cord involvement	15 mos.	Birth	O.	Better	No	D. 2½ yrs.
31	Councilmann and Dunn[8]	No cord involvement	6 mos.	3 wks.	O.	Worse	No	D. 6½ mos.
32	Bliss[5]...............	No necropsy	25 mos.	10 mos.	W-H.	Worse	Yes	D. 2½ yrs.
33	Bibergeil[15]..........	No necropsy	5½ yrs.	1 yr.	W-H.	Better	Yes	Lived
34	Bibergeil[15]..........	No necropsy	3½ yrs.	1 yr.	O.	Better	Yes	Lived
35	Foot...............	No necropsy	3 mos.	Birth	O.	Worse	Yes	D. 4 mos.
36	Reuben[14]...........	No necropsy	6 mos.	Birth	O.	Better	Yes	D. 10 mos.
37	Reuben[14]...........	No necropsy	10 wks.	Birth	O.	No improvement	Yes	D. 4 mos.
38	Reuben[14]...........	No necropsy	3½ mos.	Birth	O.	Better	Yes	Died
39	Pearce[32]...........	No necropsy	22 mos.	Birth	O.	No improvement	Yes	L. 22 mos.
40	Pearce[32]...........	No necropsy	22 mos.	1 yr.(?)	O.	Better	Yes	L. 22 mos.
41	Pearce[32]...........	No necropsy	7 mos.	Birth	O.	No improvement	Yes	L. 8 mos.
42	Pearce[32]...........	No necropsy	7 mos.	Birth	O.	No improvement	Yes	L. 8 mos.

W-H. signifies Werdnig-Hoffmann; O. signifies Oppenheim.

* Other cases in same family started 4 weeks, 6 months 6 weeks.

18. Werding: Arch. f. Psychiat. **24**: 76, 1894.
19. Wimmer: Arch. f. Psychiat. **42**: 1907.
20. Habermann: Am. J. M. Sc. **139**: 383, 1910.
21. Hoffmann: Deutsch. Ztschr. f. Nervenh. **10**: 292, 1897.
22. Sorgente, quoted by Collier and Wilson: La Pediat. **24**: 355, 1916.
23. De Villa: Arch. de méd. d. Enf. **19**: 137, 1916.
24. Skoog: J. A. M. A. **55**: 364, 1910.
25. Von Ritte: Jahrb. f. Kinderh. **59**: 224, 1904.
26. Porter, quoted by Spiller: Brain **30**: 75, 1913.
27. Collier and Holmes: Brain **32**: 269, 1909.
28. Baudouin: Semana méd., May 22, 1907, p. 241.
29. Thomson and Bruce, quoted by Batten: Brain **20**: 536, 1897.
30. Griffith and Spiller: Am. J. M. Sc. **142**: 165, 1911.
31. Foot: Am. J. Dis. Child. **5**: 359 (Sept.) 1913.
32. Pearce, N. O.: Personal communication: To be published.

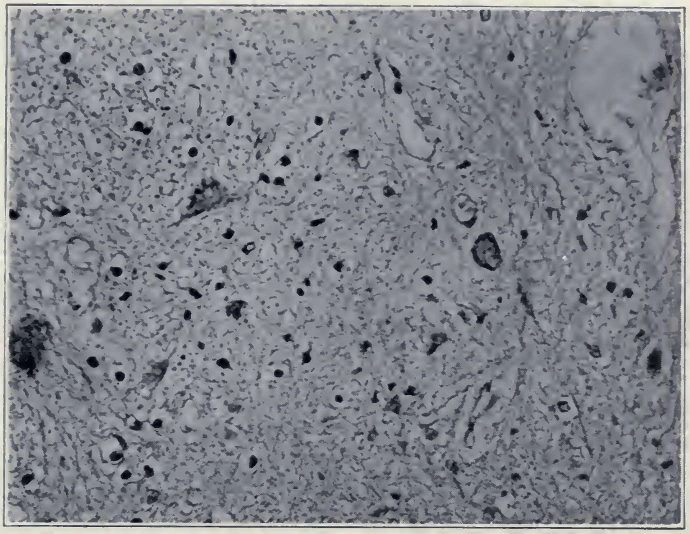


Fig. 1.—Area from the anterior horn in the thoracic cord. The nerve cells are greatly reduced in number, and many of them show extreme atrophy and disintegration.

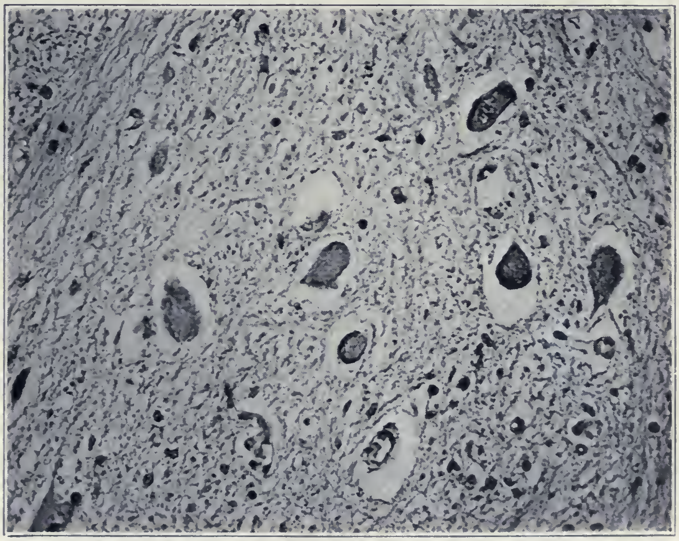


Fig. 2.—Area from Clark's column in the thoracic cord. (Same magnification as Figure 1.) The cells of this group are only slightly affected. The spaces around the cells are probably artefacts.

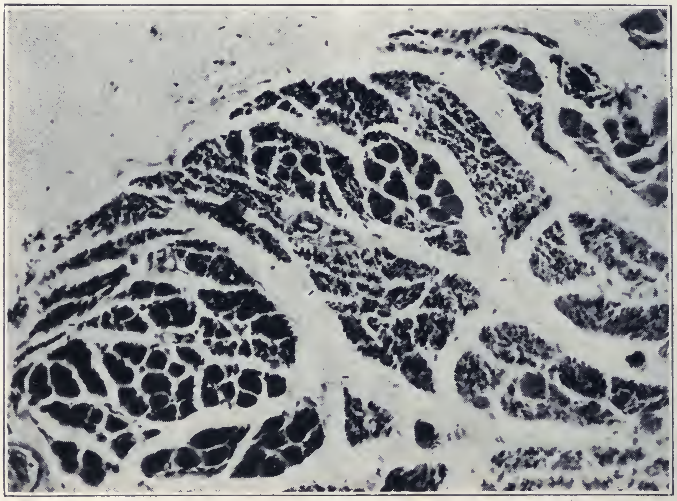


Fig. 3.—Area from biceps femoris muscle (low magnification).

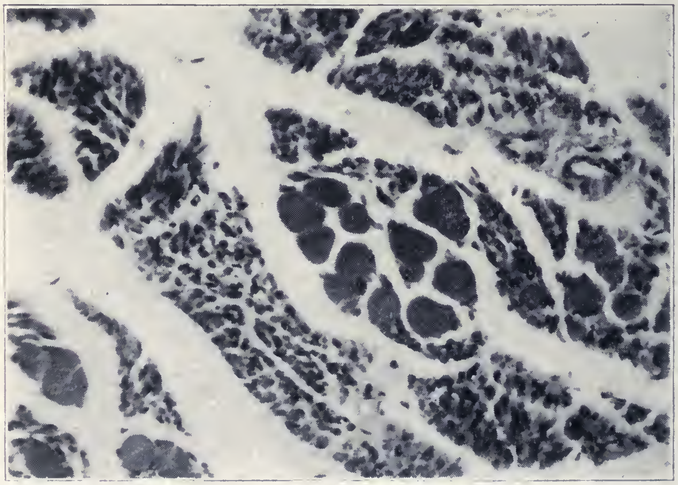
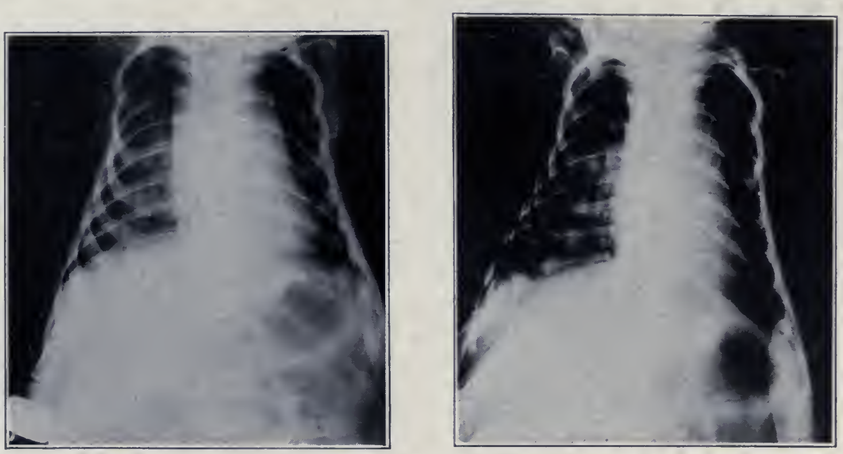


Fig. 4.—Higher magnification of an area from Figure 3.

Spinal Cord.—Meninges show no gross evidence of disease. No abnormalities in the shape of the cord. No certain evidence of disease noted on transverse sections observed with the naked eye.

Muscles.—Muscles of back and ileopsoas muscles also show marked atrophy.

Microscopic Examination.—Spinal cord: There are no changes at any level of the cord in the posterior horns. In the cervical portion there is no certain decrease in the number of nerve cells in the anterior horns, but there are a few very small cells, apparently atrophic. In the thoracic cord there is a striking decrease in the number of nerve cells in the anterior horns; and the few cells present are usually very small. Only an occasional cell of normal size is to be seen (Fig. 1). The cells in the intermediate area between the anterior and posterior horns are atrophied, but not noticeably reduced in number. The atrophy is not symmetrical, being more extensive on one side of the cord than on the other. In the lumbar cord the lesions are about the same as in the thoracic. There are no lymphocytic infiltrations or hemorrhages in any part of the cord. Sections stained by Weigert's myelin sheath method show a moderate reduction of medullary sheaths in the fasciculus gracilis.



Figs. 5 and 6.—Roentgenogram showing characteristic deformity of chest and enlargement of thymus.

Sections of the psoas and biceps cruris muscles were studied. The changes in each of these muscles consist in a marked atrophy of nearly all the muscle fibers. Some fasciculi are composed entirely of atrophic fibers; others contained both normal and atrophic fibers. Occasionally a fasciculus is seen which is composed mainly of normal fibers (Figs. 3 and 4). The difference in size between the normal and the atrophic fibers is very striking. The normal fibers average about 4 microns in diameter, while the atrophic fibers vary from 0.5 to 1.5 microns. The measurements were made from paraffin sections.

On microscopic examination the lungs show marked atelectasis. The heart, spleen, liver and kidneys show normal histologic structure.

The thymus shows a simple hyperplasia. There is a thinning of the cortex and medulla of the suprarenals.

Diagnosis. — Spinal muscular atrophy; atelectasis of lungs; hypertrophy of thymus.

Comment.—The enlarged thymus is of interest for two reasons: first, because roentgenograms taken at the first examination showed a broad shadow in the upper thorax, but it is not typical of an enlarged thymus (Figs. 5 and 6); second, because other authors (Pollak,[16] Councilmann and Dunn[8]) report a similar condition. Smith,[17] reporting the visceral findings on Spiller's case, shows enlargement of Hassal's corpuscles.

The unusual features of this case are: it is not only familial, but evidently hereditary (family history of muscular dystrophy). The second important feature is that the first baby, which died at the age of 3 months, presumably was a true case of amyotonia congenita, since the condition was probably present at birth and tended to improve up to the time of death. The second case was a typical Werdnig-Hoffmann. It was not present until the child was 6 weeks of age, grew progressively worse and was familial. With the exception of the doubtful cases of Bibergeil,[15] these are the only cases on record of the existence of a probable Oppenheim's and Werdnig-Hoffmann's disease in the same family.

CONCLUSION

From a review of the literature and our own case, the conclusion seems justified that amytonia congenita (Oppenheim) and infantile spinal progressive muscular atrophy (Werdnig-Hoffmann) are extreme types of the same disease; that they are probably both related to the group of myopathies represented by Erb's juvenile form of muscular dystrophy and the hereditary form of Leyden and Moebius.

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16. Pollak: Arch. f. Kinderh. **53**:373, 1910.
17. Smith, Allan J.: Am. J. M. Sc. **142**:165, 1911.

CONGENITAL ATRESIA OF THE ESOPHAGUS

WITH REPORT OF A CASE *

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Congenital anomalies of the upper digestive tract are not as infrequent as is generally supposed. Plass [1] found 204 references in the literature and was able to verify 137 cases from the original articles. Besides these he found thirteen cases which he could not verify on account of incorrect references or inaccessibility of the original article. He does not include any references later than 1917, and since that date several cases have been reported. Cautley,[2] Apfel,[3] Crowdy [4] and Huntington [5] have each described one case, while Brenneman [6] reported four new cases. In a discussion of Griffith's paper read before the American Pediatric Society in 1908, Dr. Putnam of Boston reported a case which has escaped notice.

Cautley's article contains a large number of references and in order to bring the literature up to date, I have appended to the references quoted in this paper a list of Cautley's references which do not appear in the Plass biography,[7] several of which I have been able to verify from the original paper. There are now reported more than 150 cases not including about twenty-eight cases which could not be confirmed.

The case which I desire to report is typical of the great majority of these malformations.

REPORT OF CASE

Dr. C. A. Pitts of Albany called me in consultation May 4 to see a baby which he had delivered May 2. The mother was a primipara and the labor was

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* Read before the American Pediatric Society, May-June, 1920.

[1] Plass: Johns Hopkins Hosp. Rep., 1919.

[2] Cautley: Brit. J. Child. Dis. **14**:1 (Jan.-March) 1917.

[3] Apfel: New York M. J. **108**:108 (July 20) 1918.

[4] Crowdy: J. M. Research **38**:469 (July) 1918.

[5] Huntington, Young and Foot: Boston M. & S. J. **180**:354 (March 27) 1919.

[6] Brenneman: Am. J. Dis. Child. **16**:143 (Sept.) 1918.

[7] Heath: Complete Absence of the Esophagus, London Med. Gaz. **26**:543; Tiedeman: Anatomie Kopfloser Missgeburten (Quoted by Schoeller); Kathe: Double Esophagus, Virchows Arch. **190**:78, 1907; Cannan and Berg: Atresia, Arch. gén. de med., p. 79, 1826; Edington: Glasgow M. J. **80**:16, 1913; Guillemet: Gaz. méd de Nantes **24**:576, 1906; Keith: A Demonstration of Fourteen Specimens from Museums of London Hospitals. (Probably individual cases reported elsewhere.) Brit. M. J. **1**:301, 1910; Pagenstecher: Siebold's J. f. Geburtsh. **19**:112, 1830; Richter: Surg., Gyn. & Obst. **17**:397, 1913; Schwalbe: Morph. der Missbildungen des Menschen und der Tiere, p. 777, 1912.

uneventful. The baby was well nourished and strong. It was observed when the baby was placed on the breast that the milk returned through the nose and thick mucus stained with dark brown material came out of the nose and mouth. Whenever she attempted to nurse she would have violent attacks of coughing and choking and expel both the milk and this thick brown stained mucus. The same thing would occur when she was given water in a bottle. Meconium was freely passed by the bowels and urine was voided normally. The temperature was elevated, from 102 to 103 F., and the chest was filled with coarse moist râles, but there was no dullness. The child appeared to be hungry and suckled vigorously when placed on the breast, but after a few swallows the milk came out of the nostrils. A small catheter was passed by the mouth, but it met with an obstruction, and on further pressure the catheter doubled up and the end appeared in the mouth. A smaller catheter passed through the nose met with the same result. It was decided to have a roentgenogram made to determine whether surgical procedure would relieve the condition. The plates made by Dr. Dinegar showed that the esophagus ended in a culdesac and that surgery offered no relief. Figure 1 illustrates the distance which the catheter could be passed and Figure 2 shows the culdesac filled with a barium mixture. These, so far as I can find, are the only roentgenograms which have been taken of this condition.

The diagnosis was simple. An operation was not advised. Two days later the baby died.

NECROPSY REPORT

The postmortem examination was made at the Bender Laboratory, May 6, 1920, by Dr. Ellis Kellert.

Frances H., age 4 days, 15 hours postmortem; body weight, 3,120 gm.; body length, 55 cm.

The body is that of a fairly well nourished, new-born female infant. Rigor mortis is absent, and there is marked lividity in the dependent parts. Externally the body is normal.

Peritoneal Cavity.—The surfaces are normal and smooth, moist and glistening. The mesenteric lymph nodes are not enlarged. The appendix is normal. The cecum is distended with meconium. There is no displacement nor abnormality of the abdominal viscera.

Pleural Cavities.—Normal.

Pericardial Cavity.—Normal.

Heart.—Normal on inspection.

Lungs.—They are slightly collapsed and deeply congested, with pale and dark red mottlings. The right middle lobe is somewhat atelectatic. On the left side the upper lobe is divided into two portions simulating three lobes to the right lung. Numerous small irregular hemorrhagic areas are present throughout. The thoracic organs and organs of the neck are removed in toto, together with the stomach.

Gastro-Intestinal Tract.—The tongue and mouth appear to be normal. The esophagus, from the tongue to a point 6 cm. below the uvula, presents a somewhat thickened wall and ends abruptly in a blind pouch. The extremity is rounded, and does not even show a fibrous connection with the lower esophagus. The stomach is normal in size and is filled with blackish-green material resembling meconium. The lower portion of the esophagus is present and in passing a probe upward it emerges through the larynx. On dissection, the lower half of the esophagus is found to be normal in appearance. It opens directly into the trachea at the bifurcation, the walls of the esophagus blending imperceptibly with those of the trachea. The trachea is filled with blood, mucus and material

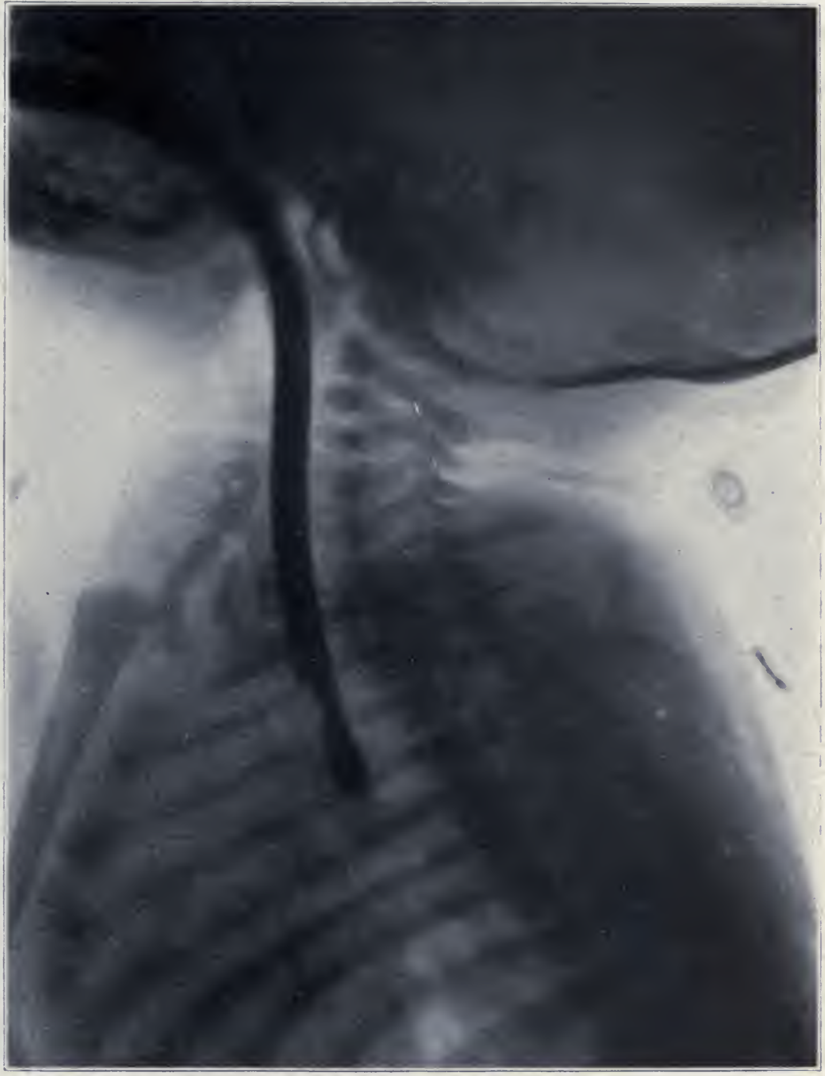

Fig. 1.—Catheter is introduced as far as possible.

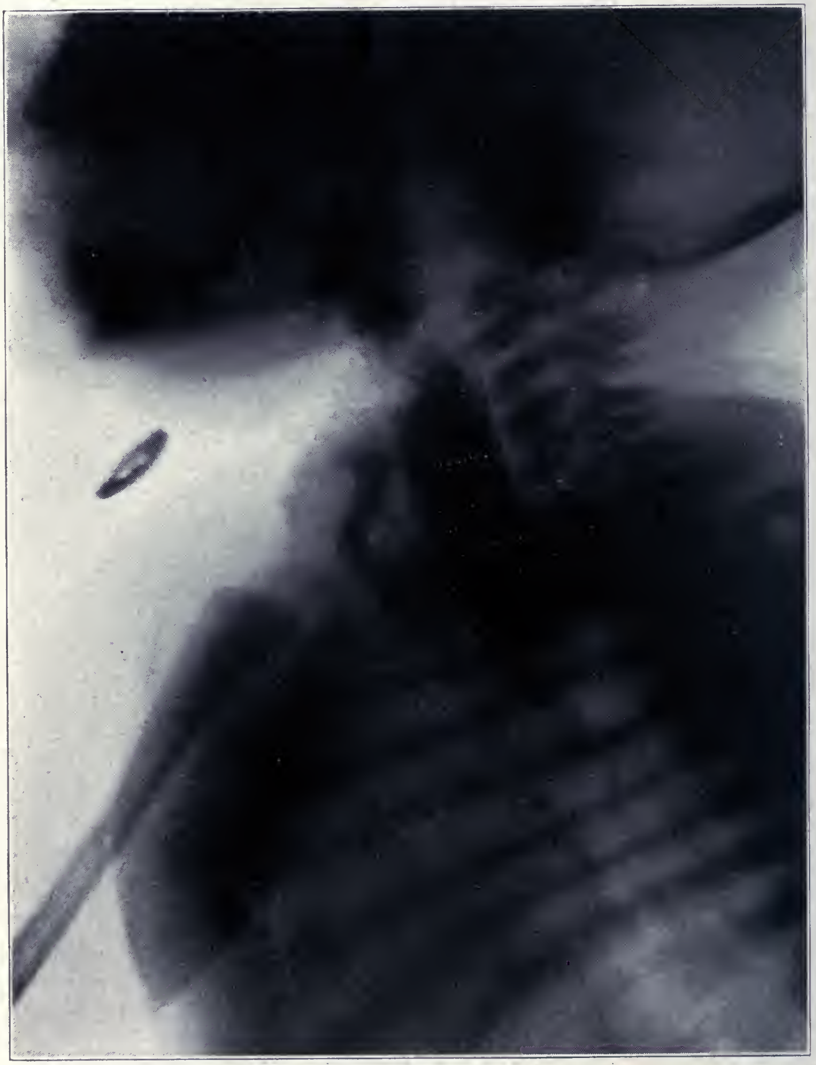

Fig. 2.—Barium in culdesac shows its size and extent.

from the stomach. The pylorus is slightly thickened, but there is no obstruction. The small and large intestines are normal throughout. The sigmoid is very mobile and free.

Genital Organs.—Normal.

Spleen.—Normal in size, shape and appearance.

Liver.—Normal.

Kidneys.—Normal. The lobulations are very distinct.

Suprarenals.—Normal.

Anatomic Diagnosis.—Atresia of esophagus. Congenital defect, with lower esophagus terminating in the trachea at the bifurcation. Early bronchopneumonia. Anomaly of left lung—three lobes.

The main points of interest in this case are the absence of a fibrous connection between the culdesac and the lower portion of the esophagus, the three lobes of the left lung and no other anomalies in the gastro-intestinal tract.

A very complete classification of esophageal malformations was made by Ballantyne[7a] from a study of the literature.

1. Complete absence of the esophagus, its place being taken by a muscular band stretching from the pharynx to the cardiac end of the stomach.
2. Termination of the esophagus in a simple culdesac.
3. Termination of the esophagus in a culdesac, the lower rudiment of the canal communicating with the trachea or bronchi.
4. Tracheo-esophageal fistula, the esophagus being otherwise normal.
5. Membranous obstruction of the esophagus.
6. Presence of esophageal diverticula.
7. Duplicity of the esophagus.

This case comes under the third type, which comprises more than 75 per cent. of all the reported cases. This points to some common embryonic origin. Zeit[8] has shown that the separation between the digestive and respiratory tract is complete at the end of the first month of fetal life. These anomalies are probably the result of an insufficient or faulty separation through lack of proper septum formation.

The first recorded case of malformation of the esophagus is one reported by Durston[9] in 1670. This case is referred to by Cautley but the original article is not available in this country. It was a case in which there was a culdesac and union between the two portions of the esophagus by a fibrous cord. Blasius[10] published a case of double esophagus in 1674.

[7a] Ballantyne: Antenatal Pathology of the Embryo, 1905, p. 462.

[8] Zeit: J. M. Research **27**:1277, 1912.

[9] Durston: Collert. Acad. Part. etrang., 1670, Tab. II, p. 283. (This reference was quoted by Crozer Griffiths.)

[10] Blasius: Observata anat. pract. in homine. Ludg. Batav. et Amster., 1674, Tab. XV, Fig. 6.

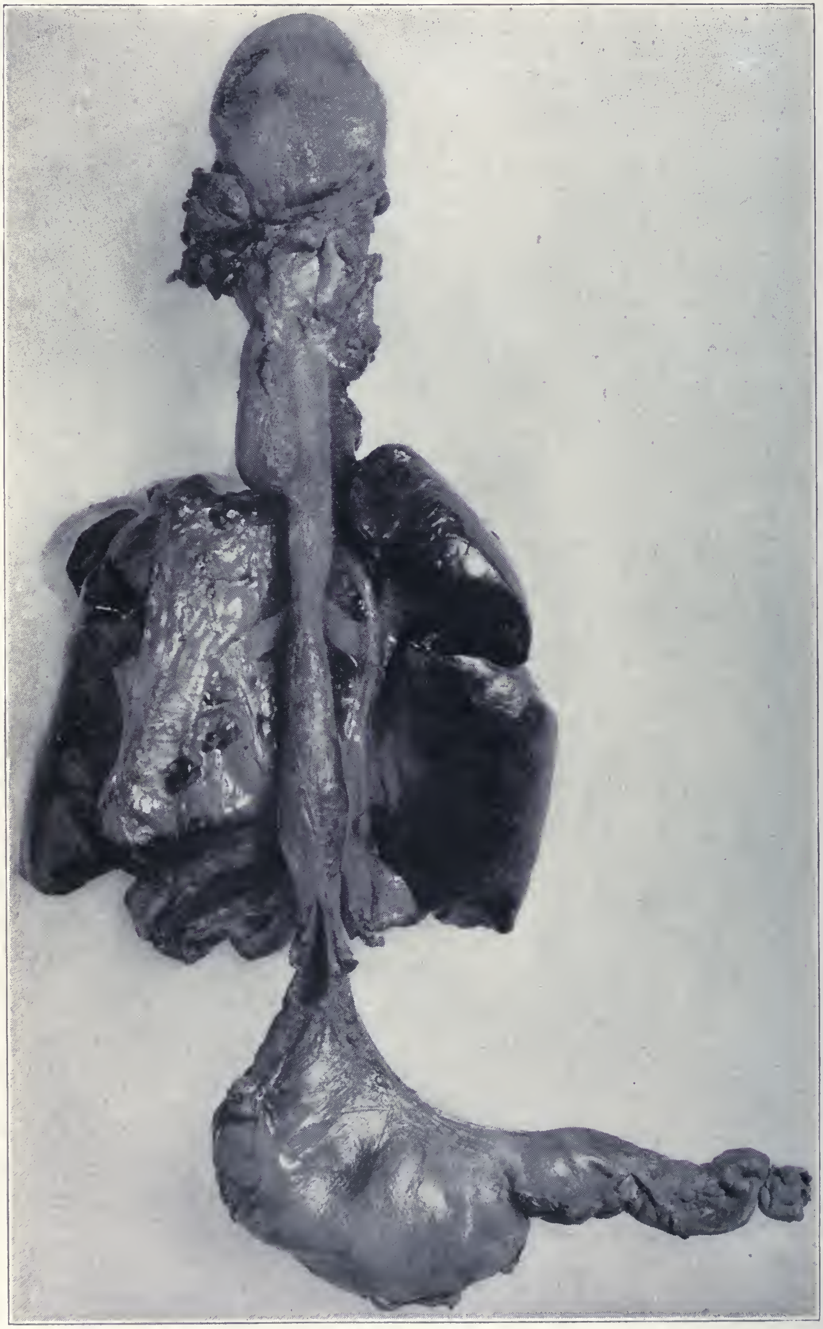

Fig. 3.—Anatomic relations of culdesac and trachea.

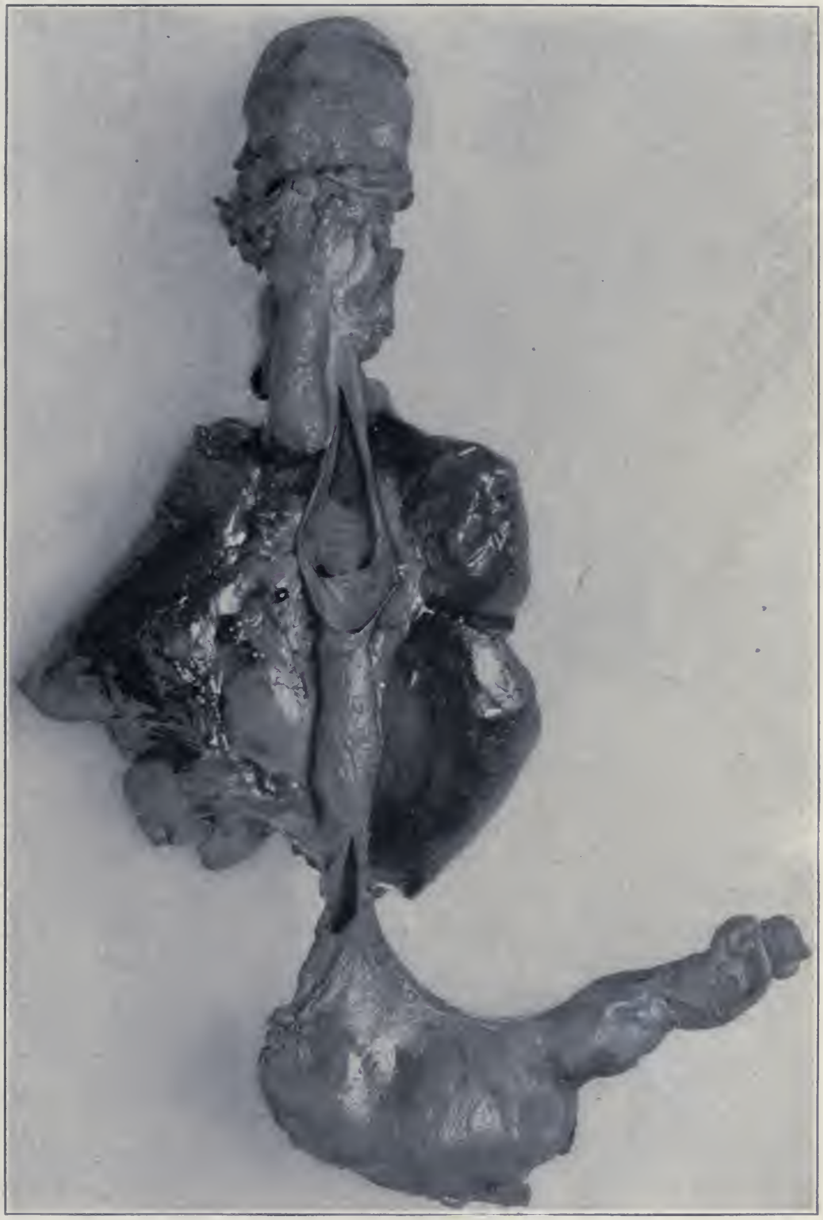

Fig. 4.—Opening is shown of lower part of esophagus in the trachea and absence of connection between upper and lower parts.

A very typical case was reported by Thomas Gibson[11] in 1696. Plass quotes this case, which is so quaintly described that it bears repetition.

> About November, 1896, I was sent for to see an infant that could not swallow. The child seemed very desirous of food and took what was offered it in a spoon with greediness, but when it went to swallow it was like to be choked, and it fell into a struggling convulsive sort of a fit upon it. It was very fleshy and large and was two days old when I was called to it, but the next day it died.
>
> The parents being willing to have it opened, I took two physicians and a surgeon with me. On opening the abdomen first, the guts had some of the meconium still in them, though the child had gone two or three times to stool. The stomach had in it a pretty deal of a slimy sort of liquid (or jelly rather), somewhat like thick (strained) water-gruel. I shall not mention observations upon other parts of the abdomen, as being not to our present purpose.
>
> Then we cut open the thorax and taking out the gullet (with the windpipe, lungs, etc.) continued to the stomach. Then we made a slit in the stomach and put a pipe in its upper orifice, and blowing, we found the wind had a vent, but not by the top of the gullet. Then we carefully slit up the back side of the gullet from the stomach upwards, and when we had gone a little above half way toward the pharynx we found it hollow no further. Then we began to slit it open from the pharynx downwards, and it was hollow till within an inch of the other slit, and in the imperforate part it was narrower than in the hollowed. This isthmus (as it were) did not seem to ever have been hollow, for in the bottom of the upper and to top of the lower cavity there was not the least print of any such thing, but the parts were here as smooth as the bottom of an acorn cup.
>
> Then searching which way the wind had passed when we blew from the stomach upwards, we found an oval hole (half an inch long) on the fore side of the gullet opening into the aspera arteria, a little above its first division, just below the lower part of the isthmus above mentioned.

Recent literature does not contain any clearer or more accurate description of this condition.

DR. THOMAS GIBSON

A few words concerning Dr. Thomas Gibson may be of interest in this connection. He was born in 1647 and died in 1722. He was a general practitioner, but wrote the most popular book on anatomy of that day, the first edition appearing in 1682, and the sixth edition in 1703. This book was entitled "The Anatomy of Humane Bodies Epitomized," and a copy of the sixth edition is in the Surgeon General's Library in Washington. Dr. Gibson was "physician-general" to the British Army in 1718-1719. An interesting sidelight on his character is found in the diary of Thomas Hearne of Oxford under date of September 8, 1717, which shows that he married a granddaughter of Oliver Cromwell.

> Sept. 8. On Saturday (Sept. 5) came to Oxford two of the daughters of Richard Cromwell, son of Oliver Cromwell, protector, one of which is married to Dr. Gibson, the physician, who writ the Anatomy; the other is unmarried.

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[11] Gibson: The Anatomy of Humane Bodies Epitomized, Ed. 6, 1703.

> They are both Presbyterians, as is also Dr. Gibson, who was with them. They were at the Presbyterian meeting-house in Oxford on Sunday morning and evening; and yesterday they, and all the gang with them dined at Dr. Gibson's, provost of Queen's College, Oxford, who is related to them, and made a great entertainment for them, expecting something from them, the physician being said to be worth 30,000 libs. They went from Oxford after dinner.

The recognition of these cases is not difficult and the passage of a small catheter establishes the diagnosis, which can be further confirmed by the roentgen ray.

Treatment is most unsatisfactory. No case has recovered or been benefited in the slightest way by either surgical or medical treatment. Brenneman [6] gives a full discussion of surgical methods which may be employed and his conclusion is that "surgical procedures have so far only served to end more quickly a hopeless situation."

OBSERVATIONS ON THE CAPACITY OF THE STOMACH IN THE FIRST TEN DAYS OF POSTNATAL LIFE

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In the transition from intrauterine to extrauterine life few organs of the body are more affected than the stomach. The change influences many characters of the organ's morphology, and the position, the mass, the finer structure, and particularly the capacity are rapidly modified and adjusted to the new conditions and functions of postnatal life.

The changes in gastric capacity in this period of transition have not been studied very intensively. As early as 1856 Guillot [1] published some data regarding physiologic gastric capacity in the first few days of extrauterine life and this was followed somewhat later by a more extensive study by Bouchaud.[2] Since that time further information on the subject has been published by Hillebrand,[3] Kruger,[4] Ssnitkin,[5] Cammerer,[6] Tuley,[7] Jaschke,[8] Landois [9] and others. The figures presented in most of these studies are not extensive, and are usually incidental to more general studies of metabolism in the neonatal period. Much of the early work is no longer of more than historic value because the observations were made under conditions which no longer obtain in modern infant feeding. Regarding anatomic capacity in this period, we have still less accurate information, the only extensive series of measurements being that of Alliot[10] on newborn children.

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[1] Guillot, N.: De la nourrice et du nourrisson, Union méd., 1852, p. 61.

[2] Bouchaud: De la mort par inanition et études experimentales sur la nutrition chez le nouveau-né, Thèse, Paris, 1864.

[3] Hillebrand, F.: Untersuchungen über Milchzufuhr und über die Jodkaliumausscheidung des Saüglings, Arch. f. Gynäk. **15**:453, 1885.

[4] Krüger, G.: Ueber die zur Nährung Neugeborener erforderlichen Milchmengen mit Rücksicht auf die Gewichtsveränderungen der Kinder, Arch. f. Gynäk. **7**:59, 1875.

[5] Ssnitkin, N.: (The Quantity of Breast-Milk Consumed by Sucklings), Allg. med. Centr. Ztg. **45**:317, 1876.

[6] Cammerer, W.: Der Stoffwechsel eines Kindes im ersten Lebensjahr, Ztschr. f. Biol. **14**:383, 1878.

[7] Tuley, H. E.: Observations on the Capacity of the Stomachs of Infants Under Ten Days of Age, Arch. Pediat. **10**:423, 1893.

[8] Jaschke, R. T.: Neue Erfährungen in der Technik der Ernährung sowie zur Physiologie und Pflege des Neugeborenen, Monatschr. f. Geburtsh. u. Gynäk. **35**:60, 1912.

[9] Landois, F.: Zur Physiologie des Neugeborenen, Monatschr. f. Geburtsh. u. Gynäk. **22**:194, 1905.

It has been pointed out recently that, during the greater part of the suckling period, there exists a fairly definite and constant relation between the anatomic capacity of the stomach, as determined postmortem, and the physiologic capacity as ascertained by weighing the child before and after feeding.[11] And it has been found that the capacity of the stomach increases at a very definite rate in early life despite the numerous fluctuations due to differences in physical constitution and to varying physiologic factors. It is the purpose of the present paper to trace the changes which these measures of gastric capacity undergo in the neonatal period, to ascertain the main factors which influence them, and to determine, in as far as possible, how soon after birth the relations and the rate of growth in capacity which are characteristic of the suckling period are established.

Through the kindness of Dr. J. P. Sedgwick, chief of the department of pediatrics, we have had access to the records of the Pediatric Section of the Elliot Memorial Hospital of the University of Minnesota. From these we have taken the records of the amount of individual feedings, as determined by weighing before and after nursing, of 323 children during the first ten days of life. In all we secured 14,571 individual records of physiologic gastric capacity as determined by this method. The distribution of these records according to days and to the birth weights of the individuals observed is shown in Table 1. To avoid confusion we have not included a statement of the number of cases in later tables but this record can be ascertained in all cases by reference to Table 1.

Our study was limited to children having a birth weight of 2,000 gm. or over, and no twins were included in the group. Otherwise the cases were taken seriatim from the hospital records. In this group there were 187 males and 136 females. The average weight at birth of the males was 3,349 gm. and of the females 3,254 gm. These figures are somewhat below the averages determined by Taylor[12] in his study of the new-born of this same clinic, but this discrepancy is probably due to the fact that Taylor, desiring to establish a norm for full term children, excluded, as far as possible, all prematures.

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10. Alliot, L.: La capacité stomicale du nouveau-nè, Thèse, Paris, 1905.

11. Scammon, R. E.: Some Graphs and Tables Illustrating the Growth of the Human Stomach, Am. J. Dis. Child. **17**:395 (May) 1919.

12. Taylor, R.: The Measurements of 250 Full-Term, New-Born Children, Am. J. Dis. Child. **17**:353 (April) 1919.

The average weight of the new-born in this same clinic as determined by Ramsey and Ally,[13] studying 300 cases, was 3,391 gm. for males and 3,276 gm. for females.

The children were breast fed five times per day, but many babies did not secure their full quota of feedings on the first day as is indicated by the small totals both of cases and feedings in column 2 of Table 1. After the first day the number of missed feedings was negligible.

TABLE 1.—Material Used in the Study of Physiologic Gastric Capacity *

Age in Days	Number of Cases and Number of Feedings					
	Group I 2,000 to 2,500 Gm. Birth-Weight (Aver. 2,260 Gm.)	Group II 2,500 to 3,000 Gm. Birth-Weight (Aver. 2,840 Gm.)	Group III 3,000 to 3,500 Gm. Birth-Weight (Aver. 3,246 Gm.)	Group IV 3,500 to 4,000 Gm. Birth-Weight (Aver. 3,731 Gm.)	Group V 4,000 Gm. and Above Birth-Weight (Aver. 4,143 Gm.)	All Cases (Aver. 3,315 Gm.)
1	5	32	71	31	14	153
	(10)	(74)	(154)	(63)	(63)	(364)
2	14	63	143	75	28	323
	(65)	(311)	(698)	(370)	(135)	(1,579)
3	14	63	143	75	28	323
	(70)	(308)	(713)	(371)	(136)	(1,598)
4	14	63	143	75	28	323
	(70)	(313)	(713)	(374)	(139)	(1,609)
5	14	63	143	75	28	323
	(69)	(315)	(712)	(373)	(138)	(1,607)
6	14	63	143	75	28	323
	(70)	(314)	(714)	(373)	(138)	(1,609)
7	14	63	143	75	28	323
	(70)	(313)	(714)	(373)	(138)	(1,608)
8	14	63	142	74	28	321
	(70)	(315)	(710)	(370)	(140)	(1,605)
9	14	63	141	74	28	320
	(70)	(314)	(700)	(368)	(138)	(1,590)
10	14	59	135	71	28	307
	(62)	(279)	(614)	(331)	(116)	(1,402)
Total No. Feedings	(626)	(2,856)	(6,442)	(3,366)	(1,281)	(14,571)

* The upper figures represent the number of cases; the lower figures, in parentheses, indicate the number of feedings.

From these data was determined the average physiologic capacity, the average maximum physiologic capacity, the average capacity in per cent. of the body weight at birth, the average maximum capacity in per cent. of the body weight at birth, the average and average maximum capacity in first born and later children, the excess of the average maximum capacity over the average capacity, and the percentage increment of the average capacity and the average maximum capacity. These determinations were made for each day of the period under consideration, first for the entire series of cases and later for the same cases grouped into five classes according to birth weight.

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[13] Ramsey, W. R., and Alley, A. G.: Observations on the Nutrition and Growth of New-Born Infants. Am. J. Dis. Child. **15**:408 (June) 1918.

The average deviation and the average percentage deviation was determined for the average capacity in the group of cases having a birth weight ranging from 3,000 to 3,500 gm. The average and average maximum capacity in males and in females was also determined in this group.

Average physiologic capacity.—The average physiologic capacity, for all children having a birth weight of 2,000 gm. or over is shown in the seventh column of Table 2 and the curve labeled "B" in Figure 1 illustrates it graphically. The average physiologic capacity of such children as received feedings on the first day was 7 gm. This was almost doubled on the second day (13 gm.) and almost quadrupled on the third day (27 gm). On the fourth day the average capacity was a little more than six times that of the first day (46 gm.). After the fourth day the increase in average capacity was much less rapid, although it was still continued, and on the tenth day it was 81 gm., or about eleven and one-half times that of the first day. As these figures indicate, a curve of the average capacity in the first ten days (Curve B, Figure 1) shows two distinct segments. During the period from birth to the fifth day it rises rapidly, thereafter it is continued upward at a much less rapid rate.

TABLE 2.—AVERAGE CAPACITY OF THE STOMACH IN THE FIRST TEN DAYS OF POSTNATAL LIFE

Days	Average Physiologic Capacity (Gm.)					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	5	6	6	8	5	7
2	10	13	13	14	11	13
3	22	27	27	27	26	27
4	36	42	45	51	46	46
5	43	53	57	62	59	57
6	43	59	64	72	70	64
7	48	60	67	76	79	68
8	51	66	71	78	80	71
9	55	68	75	83	87	76
10	60	72	79	90	96	81

Average maximum physiologic capacity.—In this study the average maximum physiologic capacity has been determined by adding the sums of the largest meal ingested by each child of the series on a given day and dividing the result by the number of cases. This is a somewhat different measurement from that employed by Feer [14] and by Scammon,[11] who used the maximum meal of a given week as a basis for determining the average maximum. The value as determined by the above definition is shown in Table 3 and is represented graphically by curve "A" in Figure 1.

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[14] Feer, E.: Beobachtungen über die Nährungsmengen von Brustkindern, Jahrb. f. Kinderh. **42**:195, 1896.

Examining these figures and the graph it is seen that there is a close relationship between average and average maximum capacity. The average maximum capacity on the first day is 9 gm. This is more than doubled on the second day (22 gm.) and increases nearly fivefold on the third day (43 gm.). On the fourth day it is a little more than seven times as great as on the first day. Thereafter, as in the case of the average capacity, the gain is much slower and on the tenth day it is eleven and two-thirds times that of the first day, or 105 gm.

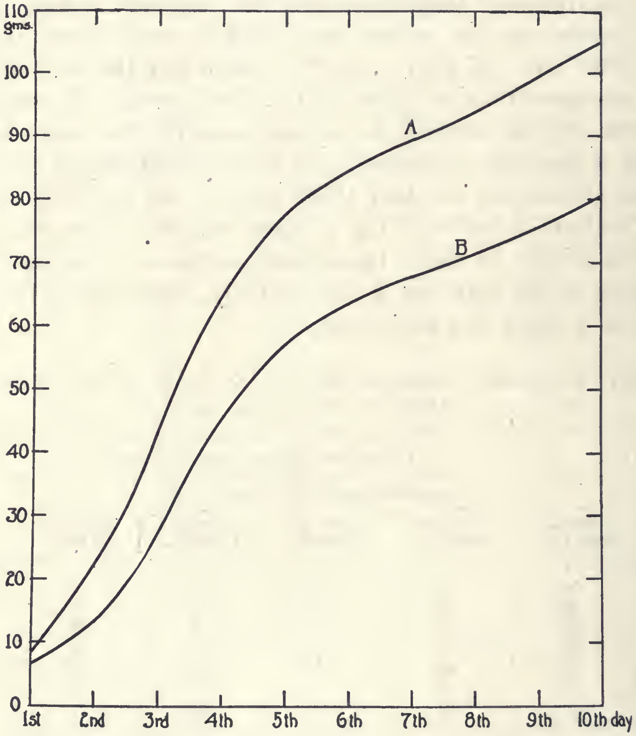

Fig. 1.—A graph showing the physiologic capacity of the stomach in the first ten days of postnatal life. A, curve of average maximum physiologic capacity; B, curve of average physiologic capacity. Based on all cases having a birth weight of 2,000 gm. or more.

The curve illustrating the changes in average maximum capacity (Curve A, Figure 1) is almost a duplicate of that of the average capacity, although all of the values are somewhat greater. It shows the same two phases as does the curve of average capacity.

Relative average and average maximum physiologic capacity.—Some interesting results are obtained if the average physiologic capacity and the average maximum capacity are calculated in terms

TABLE 3.—AVERAGE MAXIMUM PHYSIOLOGIC CAPACITY OF THE STOMACH IN THE TEN DAYS OF POSTNATAL LIFE

Days	Average Maximum Physiologic Capacity (Gm.)					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	7	9	9	10	6	9
2	18	22	23	24	19	22
3	35	41	43	45	44	43
4	53	60	65	71	65	65
5	58	70	78	85	85	78
6	63	78	86	94	88	85
7	64	82	91	98	100	90
8	65	86	94	105	100	94
9	81	87	99	107	114	99
10	84	92	104	115	122	105

TABLE 4.—AVERAGE PHYSIOLOGIC CAPACITY OF THE STOMACH IN THE TEN DAYS OF POSTNATAL LIFE, CALCULATED IN PER CENT. OF THE BODY WEIGHT AT BIRTH

Days	Average Physiologic Capacity in Per Cent. of the Body-Weight at Birth					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	0.23	0.23	0.22	0.23	0.13	0.21
2	0.44	0.45	0.39	0.38	0.26	0.39
3	0.97	0.94	0.83	0.74	0.63	0.81
4	1.61	1.47	1.40	1.38	1.11	1.38
5	1.92	1.87	1.76	1.66	1.43	1.72
6	1.90	2.08	1.97	1.93	1.69	1.95
7	2.12	2.12	2.07	2.05	1.91	2.06
8	2.26	2.33	2.18	2.09	1.93	2.16
9	2.45	2.40	2.31	2.23	2.10	2.28
10	2.66	2.52	2.42	2.42	2.33	2.43

TABLE 5.—AVERAGE MAXIMUM PHYSIOLOGIC CAPACITY OF THE STOMACH IN THE FIRST TEN DAYS OF POSTNATAL LIFE, CALCULATED IN PERCENTAGES OF THE BODY WEIGHT AT BIRTH

Days	Per Cent. of Body-Weight					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	0.29	0.32	0.27	0.28	0.14	0.27
2	0.80	0.79	0.70	0.64	0.47	0.68
3	1.54	1.46	1.31	1.22	1.06	1.29
4	2.35	2.13	2.00	1.92	1.57	1.96
5	2.57	2.46	2.40	2.28	2.06	2.35
6	2.80	2.75	2.65	2.53	2.14	2.58
7	2.84	2.89	2.79	2.63	2.42	2.73
8	2.87	3.05	2.90	2.80	2.42	2.85
9	3.59	3.08	3.06	2.87	2.75	2.99
10	3.71	3.25	3.22	3.08	2.95	3.17

of the body weight at birth. These figures are shown in Tables 4 and 5 and the curves shown in Figure 2 are their graphic expression. The average gastric capacity in the first day is equal to about one-fifth of one per cent. of the body weight. By the second day this has risen to about 0.8 per cent. and on the fourth day to nearly 1.4 per cent. of the birth weight. After the fourth day the relative gastric capacity, like the actual average capacity, increases more slowly. By the tenth day the average capacity is equal to about 2.4 per cent.

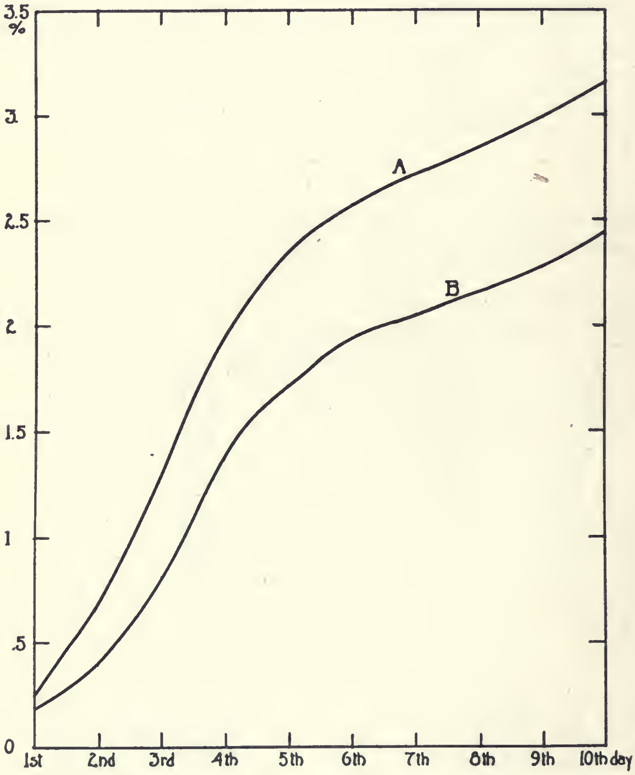

Fig. 2.—A graph showing the physiologic capacity of the stomach in the first ten days of postnatal life, as determined in per cent. of the body weight at birth. A, relative average maximum physiologic capacity; B, relative average physiologic capacity. Based on all cases having a birth weight of 2,000 gm. or more.

of the body weight at birth or about twelve times more than the average capacity on the first day.

The changes in the relative average maximum capacity are very similar to those in the relative average capacity. Starting at 0.27 per cent. on the first day, the relative average maximum rises rapidly to nearly 2 per cent. by the fourth day. Thereafter the amount increases much more slowly up to the tenth day, when it stands at nearly 3.2 per cent.

The curves based on these figures are much alike and are quite similar to those of the average and the average maximum capacity. They show the same characteristics of the rapid initial rise until the fourth day and the slower elevation from that point to the end of the period of observation (Fig. 2).

Relation between body weight and physiologic capacity.—The results which have been presented are based upon the study of the entire series of cases having a body weight of 2,000 gm. or over. The same data were studied further by arranging the cases into groups according to body weight at birth. Five of these groups were established: Group I, from 2,000 to 2,500 gm.; Group II, from 2,500 to 3,000 gm.; Group III, from 3,000 to 3,500 gm.; Group IV, from 3,500

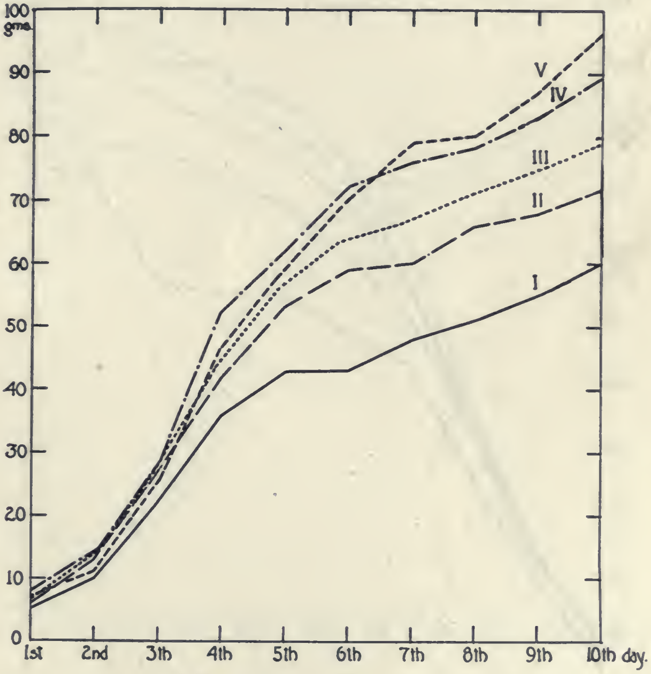

Fig. 3.—Average physiologic gastric capacity in the first ten days of postnatal life, in groups of children arranged according to birth weight. Curve I, average capacity of children with a birth weight of from 2,000 to 2,500 gm. Curve II, average capacity of children with a birth weight of from 2,500 to 3,000 gm. Curve III, average capacity of children with a birth weight of from 3,000 to 3,500 gm. Curve IV, average capacity of children with a birth weight of from 3,500 to 4,000 gm. Curve V, average capacity of children with a birth weight of 4,000 gm. or more.

to 4,000 gm. and group V, 4,000 gm. and over. The results obtained by this procedure are shown in Tables 2, 3, 4 and 5, and by the curves shown in Figures 3, 4, 5 and 6.

The absolute average gastric capacity evidently increases with the body weight in Groups I, II, III and IV (children weighing between 2,000 and 4,000 gm.). As will be seen in Table 2 and in Figure 3, there is a slight difference in favor of the groups of heavier children even on the first day and this becomes more noticeable in the latter part of the period. Group V (children having a birth weight of 4,000 gm. or over) shows a somewhat different condition. During the

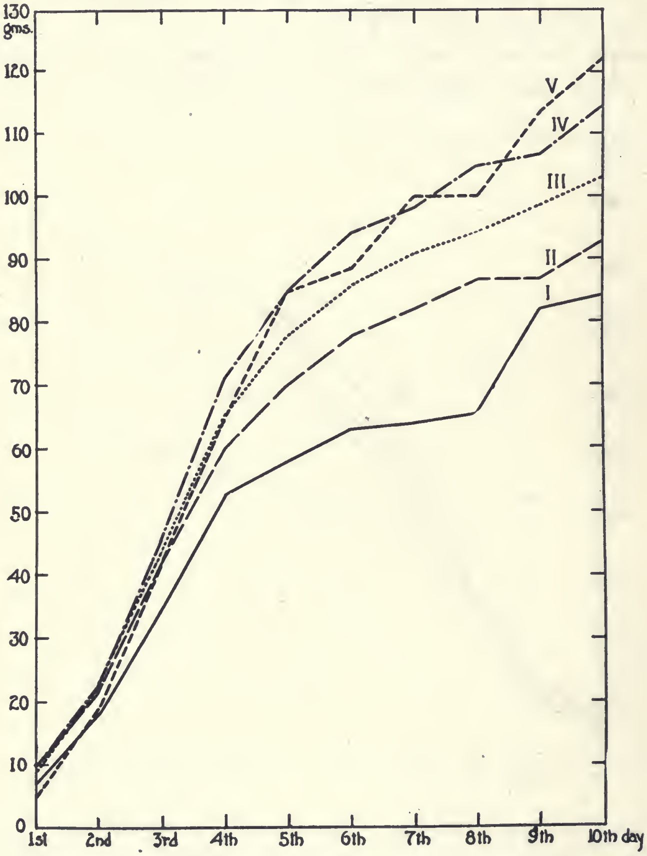

Fig. 4.—Average maximum physiologic gastric capacity in the first ten days of postnatal life, in groups of children arranged according to birth weight. Curve I, children having a birth weight of from 2,000 to 2,500 gm. Curve II, children having a birth weight of from 2,500 to 3,000 gm. Curve III, children having a birth weight of from 3,000 to 3,500 gm. Curve IV, children having a birth weight of from 3,500 to 4,000 gm. Curve V, children having a birth weight of from 4,000 gm. or more.

first three days of postnatal life the average capacity in these infants is slightly below that of the other groups of children and is only a little more than that of Group I (weighing from 2,000 to 2,500 gm.). However, the capacity of the heaviest group rises rapidly on the fourth and fifth days and on the sixth day and thereafter it exceeds that of any of the other groups.

The absolute average maximum capacity shows relations similar to those just described. It rises with the birth weight in all groups under 4,000 gm., but Group V (of 4,000 gm. and over) shows the lowest average maximum capacity on the first day. It is not until the ninth day that this value is greater in the heaviest than in the lighter groups of children.

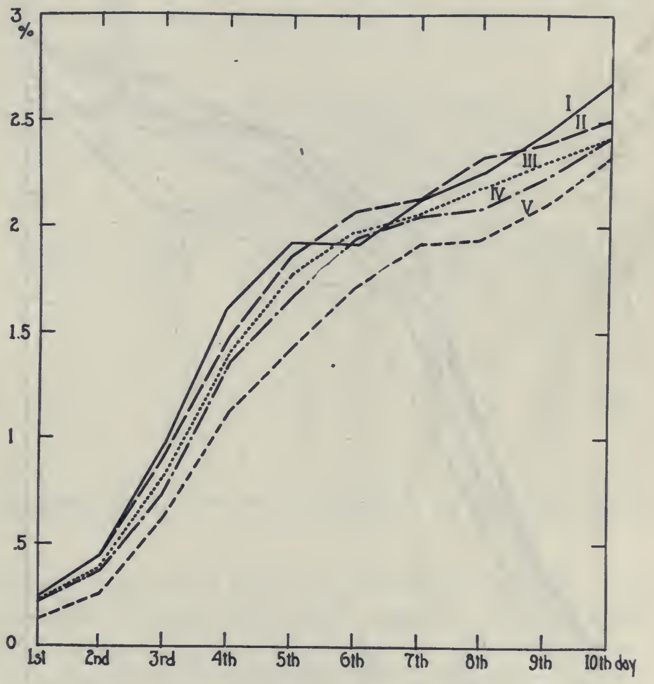

Fig. 5.—A graph illustrating the relative average physiologic gastric capacity in the first ten days of postnatal life in groups of children arranged according to birth weight. Curve I, children having a birth weight of from 2,000 to 2,500 gm. Curve II, children having a birth weight of from 2,500 to 3,000. Curve III, children having a birth weight of from 3,000 to 3,500 gm. Curve IV, children having a birth weight of from 3,500 to 4,000 gm. Curve V, children having a birth weight of 4,000 gm. or over.

The figures on the *relative* physiologic capacity, i. e., the capacity as calculated in per cent. of the birth weight, show relations which are quite different from those of absolute physiologic capacity.

On the first day the relative average capacity is approximately the same in all groups of children having a birth weight under 4,000 gm. Thereafter, with one minor exception, the relative capacity is always greater in the lighter than the heavier groups. This difference, although not very great, is practically always present. The children of Group V (of 4,000 gm. and over) have a relative capacity only a little over one-half as great as that of the lighter groups and the average value always remains far below that of the other groups during the period of observation (Fig. 5).

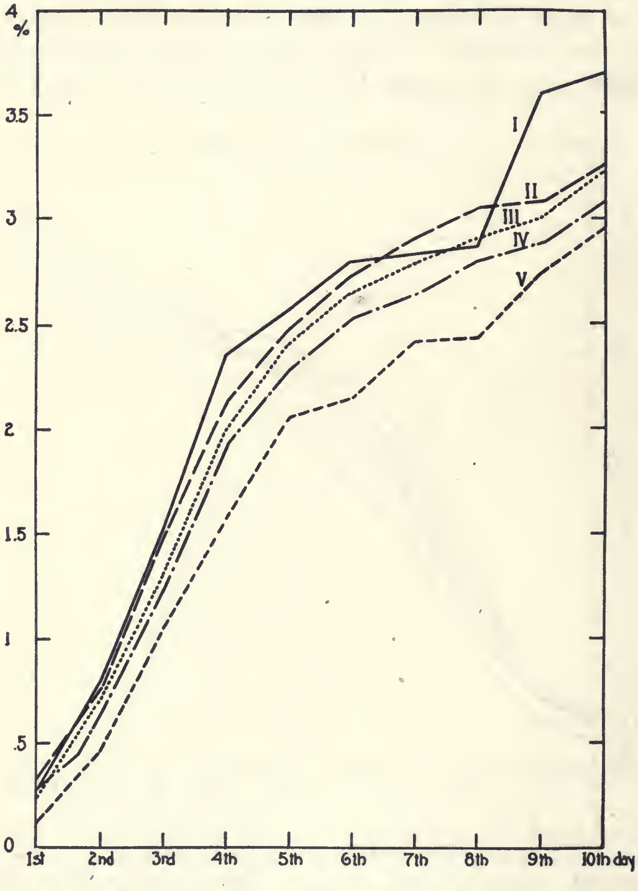

Fig. 6.—A graph illustrating the relative average maximum physiologic gastric capacity in the first ten days of postnatal life in groups of children arranged according to birth weight. Curve I, children having a birth weight of from 2,000 to 2,500 gm. Curve II, children having a birth weight of from 2,500 to 3,000 gm. Curve III, children having a birth weight of from 3,000 to 3,500 gm. Curve IV, children having a birth weight of from 3,500 to 4,000 gm. Curve V, children having a birth weight of 4,000 gm. or over.

The history of the relative maximum capacity is similar to that of the relative average capacity. The general rule that the smaller the birth weight of the group the larger the relative capacity holds true throughout except for the first day, when the relative maximum capacity is about the same in all groups of children under 4,000 gm. in weight, and for the eighth day, when this value in Group I (from 2,000 to 2,500 gm. in weight) falls below that of Group II (from 2,500 to 3,000 gm. in birth weight).

It may, therefore, be concluded that while the heavier children of this series tend to have a larger absolute physiologic capacity than do the lighter ones, this capacity does not increase directly in proportion with body size.

TABLE 6.—DIFFERENCES IN THE AVERAGE PHYSIOLOGIC GASTRIC CAPACITIES OF FIRST-BORN AND LATER CHILDREN *

Days	Differences in Capacities (Gm.)					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	+1	—1	+1	+6	+6	0
2	0	+6	—3	+4	+7	+2
3	0	+9	—5	+4	+15	+3
4	0	+6	+1	+12	+23	+5
5	—4	+3	—4	+3	+6	—1
6	+7	—1	—10	—2	+17	—1
7	+5	—4	—13	+2	+20	0
8	+8	—3	—8	+3	+19	0
9	—2	—2	—5	+2	+34	+8
10	—13	+4	—3	0	+18	+3

* Figures preceded by a minus sign indicate a greater average capacity in first born children. Figures preceded by a plus mark indicate a greater average capacity in later children.

Physiologic capacity in first-born and later children.—The average and the relative average physiologic capacity were calculated separately for first-born and for later children. This was done first for the entire series of cases and then for the several groups arranged according to birth weight. The differences between the first born and later children were then determined from these figures and are shown in Table 6. The figures in this table which are preceded by a plus sign indicate an excess in capacity of the later children over the first born, and those preceded by a minus, an excess in capacity of the first born over the later born. If Groups I to IV, inclusive, of this table are examined, it will be seen that there are no consistent differences in these values in the two classes of children. However, in Group V, having a birth weight of 4,000 gm. or over, the capacities of later children are consistently and considerably greater than those of first born infants. As the relative average capacities showed practically identical results they will not be considered here in detail.

Physiologic capacity in males and females.—The average and the average maximum capacities were determined separately for males and for females in Group III (children having a birth weight of from 3,000 to 3,500 gm.). No consistent sex difference in capacity, as determined by either of these measures, was observed.

Variability in average physiologic capacity in the neonatal period.—It is, of course, well known that the variation in the amounts ingested at single meals by young infants is very great, but apparently no attempt has been made to measure it. In order to secure some measure of this value we determined the range of variation and the average deviation and the percentage deviation in the feeding records of the group of children having a birth weight ranging from 3,000 to 3,500 gm. (Group III).

The range of variation is easily secured by determining the maximum and minimum meal of the entire series of feeding records for each day of the period of observation. This determination, while of interest, tells us little of the actual amount of variation in our material, which is much better indicated by the average deviation and the percentage deviation. The average deviation is calculated by first determining the amount that each observation differs from the average of the whole series. These amounts are then added (plus and minus signs being disregarded) and the sum is divided by the total number of cases. The result expresses the average deviation (in this case in grams). This value can be readily converted into a per cent. of the average capacity by dividing by the average of all cases and multiplying by 100.

TABLE 7.—VARIABILITY IN AVERAGE PHYSIOLOGIC GASTRIC CAPACITY IN IN THE FIRST TEN DAYS OF POSTNATAL LIFE*

Days	Number of Observations	Average Capacity, Gm.	Minimum Feeding, Gm.	Maximum Feeding, Gm.	Average Deviation, Gm.	Per Cent. Deviation
1	154	6	3	60	3.6	60.0
2	698	13	4	80	6.8	52.3
3	713	27	3	110	15.2	56.3
4	713	45	5	130	17.9	39.8
5	712	57	8	140	19.2	34.7
6	714	64	2	165	19.3	30.1
7	714	67	10	145	20.6	30.7
8	710	71	10	160	21.3	30.0
9	700	75	5	148	20.5	27.3
10	614	79	10	210	20.6	26.0

* Based upon the feeding records of children with a birth-weight ranging from 3,000 to 3,500 grams.

The results of these calculations are shown in Table 7 and are, in part, graphically expressed in Figure 7. The minimum meal during the first ten days ranges from 2 to 10 gm. and shows no particular regularity. The maximum meal was 60 gm. on the first day and rises fairly steadily to 160 gm. on the sixth day. Thereafter it is quite irregular. The average deviation rises rapidly in the first three or four days, but after the fourth day it stands between 19.2 and 21.3 gm., which is surprisingly constant considering the nature of the material. The percentage deviation in the first three days of postnatal life forms over one-half of the average capacity. It then decreases, at first rapidly and later quite slowly, during the remainder of the period. In round numbers the percentage variability in the first third of the period of observation is twice as great as in the last third.

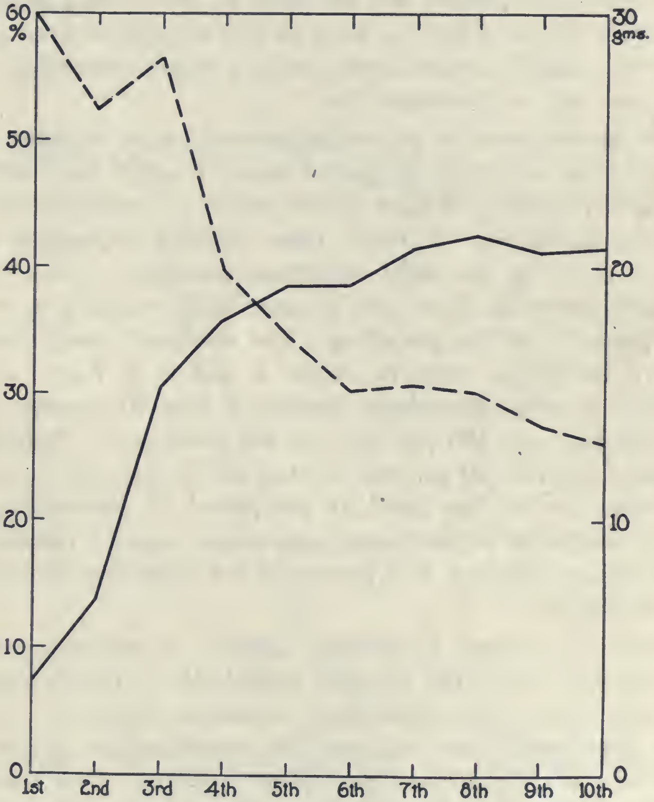

Fig. 7.—A graph illustrating the changes in variability in average physiologic gastric capacity in the first ten days of postnatal life. Curve A (in solid line), average deviation in average physiologic capacity. Curve B (in broken line), percentage deviation in average physiologic capacity. Based on the feeding records of a group of 143 children having a birth weight ranging from 3,000 to 3,500 gm.

This variability seems to have no close relation to the feeding schedule of the children. The maximum meal of the day may occur at any of the five feeding periods. In the first four days it is less frequently the first meal in the morning, while in the last six days the last meal in the evening is less often the largest one of the day. However, the differences in distribution of the maximum meal among the several feeding periods in the entire group of cases are so slight that no definite conclusion can be drawn from them.

In our entire series of cases there were forty-six instances in which a meal was missed. In eighteen cases the succeeding meal was smaller than the average; in twenty-two cases it was larger than the average, and in six cases it was the same as the average meal. The small amount of data which we have on this subject does not indicate that loss of a meal is compensated for by a larger succeeding one, in the first few days of postnatal life.

Percentage increment in physiologic capacity in the neonatal period.—The measures of growth in gastric capacity which have been described in the preceding sections of this paper are mainly in the form of absolute quantities. A much more striking exposition of the changes is given by the daily percentage increment. This value is calculated by determining the gain in capacity for each day in per cent. of the capacity of the day preceding. The results of these calculations are shown in graphic form in curves B and C in Figure 8. The increment in average physiologic capacity is over 80 per cent. on the second day and over 100 per cent. on the third day. Thereafter, it falls rapidly to about 20 per cent. on the fourth day and to less than 10 per cent. for the last third of the period of observation. The percentage increment in maximum physiologic capacity follows much the same history although it is greater at the beginning of the period (Curve B, Fig. 8).

Relation of average physiologic capacity to average maximum physiologic capacity in the neonatal period.—In a recent paper one of us pointed out that the average maximum physiologic capacity, from the third week after birth until the seventh month, is about one-half greater than the average physiologic capacity. The relation of these two values in the period of the new-born shows several striking changes. On the second day the average maximum capacity is about 25 per cent. greater than the average capacity. On the second day it is 70 per cent. greater. It then drops until the fifth or sixth day to about one-third more than the average capacity (Curve A, Fig. 8.).

The anatomic capacity of the stomach in the new-born and the neonatal period.—The anatomic capacity of the stomach in the new-born, as determined by a number of observers using a variety of methods, falls between 25 and 35 c.c. Most of the published work on anatomic capacity at birth does not include records of the individual cases and therefore is not very satisfactory. The most complete published data on this subject are those of Alliot,[10] and to these we have been able to add a small number of personal observations. The combined data available to us are shown in Table 8. The average anatomic capacity in a series of 25 new-born children ranging in birth weight from 2,000 to 4,300 gm. was 33 cc. In thirteen premature children having a birth weight ranging from 1,200 to 2,000 gm. the average capacity was 22 c.c. In new-born children having a body weight between 2,000 and 3,000 gm. the average capacity was 30 c.c.; and in those between 3,000 and 4,000 gm. body weight, 35 c.c. Three very large infants, having a body weight of 4,000 gm. or more, had an

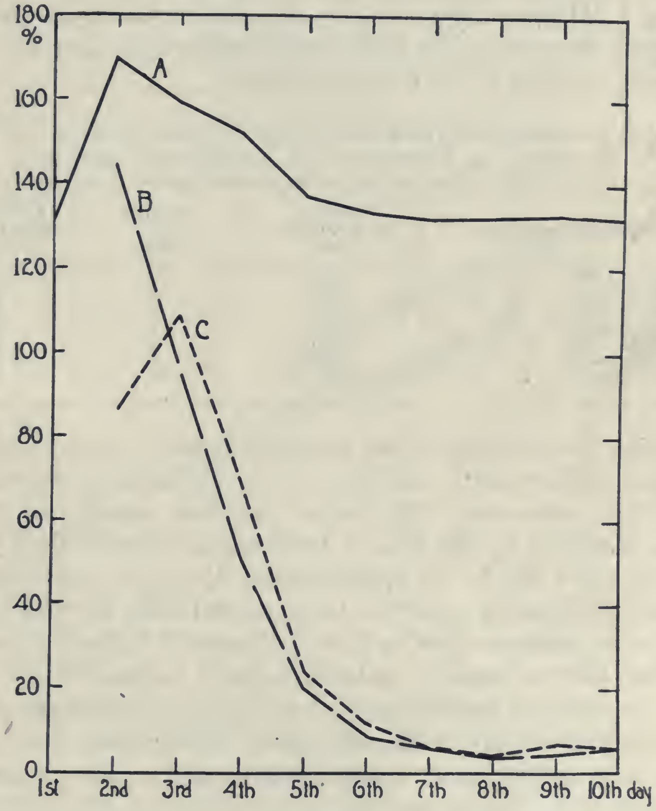

Fig. 8.—Curve A, percentage which the average maximum physiologic capacity forms of the average physiologic capacity in the first ten days of postnatal life. Based on all cases of 2,000 gm. and over. Curve B, percentage increment in the average physiologic gastric capacity in the first ten days of postnatal life. Based on all cases of 2,000 gm. and over. Curve C, percentage increment in the average maximum physiologic gastric capacity in the first ten days of postnatal life. Based on all cases of 2,000 gm. and over.

average capacity of 38 c.c. Thus the anatomic capacity at birth appears to increase somewhat with the body weight as does the physiologic capacity of the neonatal period.

The relative anatomic capacity, i. e., the capacity of the stomach calculated in per cent. of the body weight (c.c. considered equivalent to gm.), was, for this same series of cases, 1.3 per cent. in infants having a body weight below 2,500 gm,, 1.1 per cent. in children weighing between 2,500 and 3,500 gm., and 0.9 per cent. in children weighing 3,500 gm. or more. Thus the relative anatomic capacity of the stomach decreases as the body weight increases, as does the relative physiologic capacity in the neonatal period.

TABLE 8.—Average Anatomic Capacity of the Stomach in the New-Born as Determined by Zucarrelli's Method

Range of Body-Weight, Gm.	Average Body-Weight, Gm.	Number of Cases	Average Anatomic Capacity, C.c.
1,500 to 2,000	1,710	13	22
2,000 to 2,500	2,140	3	30
2,500 to 3,000	2,740	7	30
3,000 to 3,500	3,210	6	35
3,500 to 4,000	3,710	6	35
4,000 or more	4,340	3	38
2,000 or more	3,140	25	33

Detailed observations on the anatomic capacity of the stomach in the period between birth and the end of the second postnatal week are not very numerous. The average anatomic capacity of the first week, as indicated by the data of Fleishmann,[15] Froloffski,[16] Stössl,[17] Zuccarelli [18] and Rotch,[19] is approximately 45 c.c. or nearly one-third more than the capacity at birth. In the second week the data collected by these same observers and by Holt,[20] d'Astros,[21] Politzer,[22] Muggia [23] and others, indicate that the anatomic capacity is about 75 c.c. These figures are based on determinations by a variety of methods, although the majority of observations were made with Zuccharelli's method. The curve of growth in anatomic capacity in the neonatal period is shown in semidiagrammatic form in Figure 9. As will be seen from this figure, the anatomic capacity of the stomach appears to increase at a uniform rate throughout the period and there are no indications of two distinct phases of growth comparable with those seen in all of the graphs of physiologic capacity.

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[15] Fleischmann: Klinik der Pädiatrik, Wien., 1875.

[16] Froloffski: Material on the Anatomy of the Digestive Tract in Sucklings, Diss., St. Petersburg, 1876.

[17] Stössl: Semiotik des Kindesalters, 1875.

[18] Zuccarelli, P.: L'estomac de l'enfant, Thèse, Paris, 1894.

[19] Rotch, T. M.: Pediatrics, Ed. 1, Philadelphia, 1896, p. 76 et seq.

[20] Holt, L. E.: Observations on the Capacity of the Stomach in Infancy, Arch. Pediat. **7**:960, 1891.

[21] d'Astros: L'estomac de l'enfant; sa dilatation, Rev. de Mal. de l'enf. 12, 1894.

[22] Pollitzer: Ideen zur Behandlung einer wissenschaftlichen Diatetik, Jahrb. f. Kinderh. 4, 1858.

[23] Muggia, A.: La capacité e la posizione del ventricalo nei bambini, Giorn d. r. Accad. di med. di Torino, Series 4 **2**:351, 1896.

Although the growth of the anatomic capacity of the stomach in the neonatal period appears to be quite slow if compared with the growth in physiologic capacity, it is very rapid compared with the growth in fetal life. In the first week after birth the anatomic capacity increases more than it does in the entire last third of fetal life, and the absolute increase in the first two weeks of postnatal life is considerably greater than the entire prenatal growth.

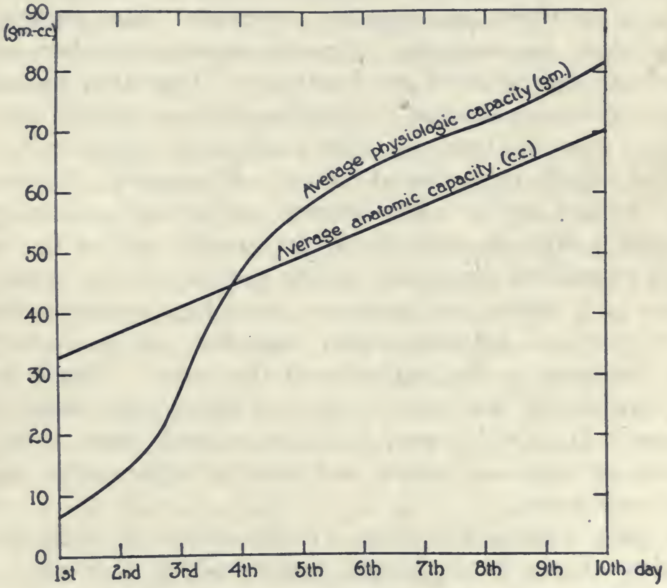

Fig. 9.—Semidiagrammatic curves illustrating the relation between the average physiologic capacity and the average anatomic capacity of the stomach in the first ten days of postnatal life.

DISCUSSION

The discussion of our data will be limited to a comparison of anatomic and physiologic capacity in the neonatal period and to a consideration of certain peculiarities of physiologic capacity during this time.

It has been pointed out by one of us (Scammon[11]) that during the greater part of the suckling period there is a close correlation between the anatomic capacity of the stomach, as determined postmortem, and the average physiologic capacity, as determined by weighing before and after feeding. The physiologic capacity, as determined by this method, was found to be approximately equal to the anatomic capacity of the organ under a pressure of between 15 and 20 centimeters of water. It was also noted that practically all of the technics used in determining anatomic capacity distend the viscus to about the same extent as does a pressure of 15 centimeters of water.

The relation between anatomic and physiologic capacity in the neonatal period is somewhat more complex than in the suckling period proper. It is represented in a semidiagrammatic fashion by the two curves shown in Figure 9. At birth the anatomic capacity of the stomach is roughly four and one-half times the physiologic capacity (on the average as 33 to 7). During the first half of the first week of postnatal life the anatomic capacity increases about one-third, while the physiologic capacity is increased about six-fold. The curves of these two measures of gastric capacity therefore converge and meet between the third and fourth day. Thereafter the anatomic capacity continues to increase at about the previous absolute rate. The physiologic capacity, however, rises much more slowly and is soon established slightly above that of the anatomic capacity. Evidently the constant relation which exists between the average physiologic and the average gastric capacity during the greater part of the suckling period is established during the middle part of the first week.

Taken as a whole, the figures on physiologic capacity which are presented here are distinctly higher than those of the earlier investigators mentioned at the beginning of this paper. This is not surprising considering that most of these workers made their observations upon infants which were fed eight or more times a day. The differences between our results and those of other recent observers are not very great.

The most noticeable feature of this series of observations is the marked change in physiologic capacity which takes place on the fourth or fifth day. This change is seen in all of the values of physiologic capacity which we have determined—in the absolute physiologic capacity both average and average maximum, in relative capacity, in percentage increments of both the average and the average maximum capacity, and in the two simple measures of variability which we have employed. In the first four days all measures of gastric capacity show a very rapid increase while in the last six days of the period of observation the increment is comparatively slow. In the first four days, also, the degree of variability in physiologic capacity is changing rapidly while in the latter part of the period it stands at a fairly constant figure.

The rapid gain in physiologic capacity of the first four days is probably no index of the actual growth of the stomach of this period since it is almost the end of this time before the physiologic capacity of the stomach equals the anatomic capacity. The figures and curves relating to this part of the period of observation are criteria of the ability of the mother to furnish food and of the ability of the infant to ingest it rather than actual measures of the growth of the stomach in cubic capacity. Similarly, the indices of variability which have been presented are measures of the variability of the above factors rather than of gastric capacity proper.

The later gain in physiologic capacity, from the fourth to the eleventh day, probably approaches much closer to the real index of the stomach's growth since it is substantially the same as the increase in anatomic capacity.

Unfortunately, we have no available data on the weight or surface area of the stomach in the first few days after birth to enable us to determine whether the growth of the organ in these respects is comparable with the changes in capacity. It is known, however, that the growth of the stomach in net weight is very great in the first postnatal months when the organ is increasing most rapidly in capacity.

As has been pointed out, our figures indicate that the absolute physiologic capacity increases, though not directly, with the birth weight of the child. This finding agrees with the earlier observations of Ssnitkin [5] on physiologic capacity. On the other hand, Holt [20] in his study of anatomic capacity, found no relation between this measure and body weight. However, his observations were made mainly on older children. That the relative physiologic capacity of groups of lighter children is greater than that of heavier groups has not, we think, been specifically pointed out previously, although several recent studies, such as those of Reicke [24] and Hammett,[25] have noted a relatively rapid rate of growth of premature infants which might be expected to be associated with a greater relative food intake. There are few published figures on the relative gastric capacity in the neonatal period. The only ones based on an extensive series of cases are those of Ssnitkin,[5] who calculated that the average meal was equal to 1 per cent. of the body weight plus 1 gm. for each day of postnatal life. This rule gives values far below those quoted in our tables despite the fact that our percentages are figured on the birth weight rather than the actual weight at the time of feeding. This discrepancy is probably due in part to the feeding methods employed in Ssnitkin's cases, and in part to the fact that his observations extended over the entire first month while ours were limited to the first ten days of postnatal life.

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24. Reicke, A.: Das Wachtum der Frühgeburten in den ersten Lebensmonaten, Ztschr. f. Kinderh. **13**:332, 1915.

25. Hammett, F. S.: The Relation Between Growth Capacity and Weight at Birth, Am. J. Physiol. **45**:396, 1918.

Our figures show no constant differences in the physiologic capacity of first born and later children, except for the group of heaviest cases. This result was unexpected for a priori one might expect that first born children would take smaller meals than later ones both because of greater birth trauma, which would limit their power of nursing, and because the mammary glands of primiparae begin to function a little later after delivery than do those of multiparae. While the difference in this later factor in multiparae and primiparae is one of hours only, according to Landois'[9] observations, still one might expect it to affect our averages slightly. It may be that our findings in this particular are due to the nature of the material studied, for it is the practice of the University Hospital to receive all primiparae for delivery while multiparae are only received when there is record of previous difficult deliveries, when pathologic symptoms are observed, or when the social conditions of the mother are adverse. By far the larger number of multiparous mothers of our series were admitted to the hospital for delivery because of adverse social circumstances. Possibly these circumstances have influenced the physical condition of the mothers to the extent of limiting the milk supply during the first ten days postpartum.

The group of heaviest children in our series (those having a birth weight of 4,000 gm. or more) show several peculiarities of gastric capacity not seen in the groups of smaller infants. These heavier children have smaller relative anatomic capacities at birth than do the lighter ones and their physiologic capacities, both absolute and relative, are smaller in the first week of life. In the early part of the second week the absolute physiologic capacity in this group rises above that of the lighter groups of children but the relative physiologic capacity remains far below throughout the period of observation. In this group, also, parity has a distinct effect on physiologic capacity, and the averages of first born children are distinctly below those of later children. We are inclined to attribute most of these peculiarities in physiologic capacity to the greater trauma which these children undergo at birth.

SUMMARY

The results of this study may be summarized as follows:

1. The average physiologic capacity of the stomach in the first day after birth is about 7 gm. This practically doubles in the second day, quadruples on the third, and increases almost sevenfold on the fourth. After the fourth day, the increase is much slower and the average capacity on the tenth day is 81 gm. or over eleven times that of the first day. The average maximum physiologic capacity increases in much the same manner as the average physiologic capacity.

It is about one-fourth greater than the average physiologic capacity on the first day and about two-thirds greater on the second. Thereafter the difference between the two measures decreases rapidly until the sixth day. After the sixth day the average maximum capacity remains about one-third more than the average capacity.

2. The relative physiologic capacity increases in much the same way as the absolute physiologic capacity. It is equal to 0.21 per cent. of the birth weight of the body on the first day, to 1.38 per cent. on the fourth day, and 2.43 per cent. on the tenth day. The relative maximum capacity is equal to 0.27 per cent. of the initial body weight on the first day, to 1.96 per cent. on the fourth day, and to 3.17 per cent. on the tenth day.

3. In the first ten days parity has no constant effect on the physiologic capacities of children having an initial body weight of from 2,000 to 4,000 gm. Sex has no effect on the physiologic capacity in this period.

4. The average deviation in physiologic capacity rises rapidly from the first to the fourth day. Thereafter it increases very slowly. The percentage deviation decreases rapidly until the fifth day and thereafter continues to drop very slowly.

5. All indices of physiologic capacity indicate that there is a distinct change in the nature of this value about the fourth day. Until this time the increase in capacity, in whatever manner it is calculated, is very rapid, thereafter it is much slower. In the first four days average deviation in capacity is increasing rapidly and percentage deviation is decreasing rapidly. After this time both of these measures change very little.

6. The anatomic capacity of the stomach at birth averages 33 c.c. This is increased about one-third in the first three or four days and is a little more than doubled in the second week. There is no indication of two definite stages in the development of anatomic capacity in the neonatal period corresponding to the two phases of physiologic capacity. Anatomic capacity and physiologic capacity approximate one another about the fourth day. Thereafter physiologic capacity runs parallel to the anatomic capacity but is slightly greater. This agrees with previous findings regarding this relation throughout the greater part of the suckling period.

7. The curve representing average physiologic capacity in the first ten days of post natal life shows two phases. The first segment, extending from birth to the fourth day, shows little relation to the actual capacity of the organ but is rather a measure of the ability of the average mother to furnish nourishment in this period and the ability of the average child to receive it. The second segment, extend-

ing from the fourth to the tenth day, is probably a fair measure of the actual increase in gastric capacity comparable with similar measures of this value made at later times in the sucking period.

8. The gastric capacities of children weighing 4,000 gm. or over at birth are somewhat different from those of infants of lighter weights. Both the average and the average maximum physiologic capacities of this group are smaller than those of lighter children in the first three or four days of post natal life but these values increase rapidly in the fifth and sixth days and before the end of the period exceed those of smaller infants. Parity has a slight but distinct effect on physiologic capacity in this group of large infants, and first born children have a smaller capacity than do the later born. The anatomic capacities of children of this group are somewhat greater absolutely but smaller relatively than in children of the lighter groups.

STUDIES IN SPASMOPHILIA

II. ELECTRICAL REACTIONS OF OLDER CHILDREN

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In the first paper of this series [1] I stated that the term spasmophilia was being used to denote that latent condition in infants one year old or less in which a heightened electrical irritability is shown by an anodal opening contraction (A O C) of less than 5 ma. and requiring less current than the anodal closing contraction (A C C), a phenomenon which Thiemich was the first to consider as spasmophilic; or a cathodal opening contraction (C O C) with less than 5 ma., known as Escherich's sign. It was further stated that for the active condition manifesting convulsions, laryngospasm, carpopedal spasm and other forms of spasm the term tetany is reserved. This classification is recommended by others, notably Langstein and Meyer.

In testing the electrical reactions of older children, one is confronted with the question: Do the same standards of electrical diagnosis for infants apply to children more than 2 years of age?

Combing an abundant literature on tetany and spasmophilia one encounters few attempts to answer this question. In 1886, Stinzig [2] established the normal value for the C C C in adults but went no farther. Von Pirquet's standards are based on a study of twenty-four children under 2 years of age and fulfill the requirement for spasmophilia if A O C is less than 5 ma. Sedgwick [3] in 1912, reported some electrical reactions on mothers of infants with tetany, and cites an A O C = 4.6 (in the mother) and greater than the A C C as "slightly spasmophilic." Two years later the same observer [4] applies electrical tests to the parents and grandparents of spasmophilic infants. Wilcox [5] in a study of infantile tetany states that "it is very difficult to define exactly the normal electrical response of childhood." His observations are on infants under 2 years of age.

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1. Von Meysenbug, L.: Studies in Spasmophilia. I. Spasmophilia and Vitamins, Am. J. Dis. Child. **20**:206 (Sept.) 1920.

2. Stinzig: Ueber Electrodiagnostische Grenzwerte, Deutsch. Arch. f. klin. Med. **39**:76, 1886.

3. Sedgwick, J. P.: Spasmophilia in Children with Illustrative Cases, St. Paul M. J., October, 1912.

4. Sedgwick, J. P.: Spasmophilia with Especial Reference to Familial Reactions and Repeated Absences, Am. J. Dis. Child. **7**:140 (Feb.) 1914.

5. Wilcox, H. B.: The Diagnosis of Infantile Tetany, Am. J. Dis. Child. **1**:393 (June) 1911.

It was apparently assumed up to this time that the electrical standards for infants were applicable to older children and adults in the diagnosis of spasmophilia. In a study of older children, Holmes,[6] in 1916, added valuable information to the subject. He tested the electrical reactions of 400 tetany-free children ranging in ages from one month to 13 years, and gives in tabular form the average values for the different ages. The average values are condensed in Table 1.

TABLE 1.—Electrical Reactions of Tetany-Free Children

Ages	No. Examined	C C C	A C C	A O C	C O C
1- 5 years....................	105	2.9	4.2	4.3	>5
5-13 years....................	172	1.7	3.7	3.1	>5

In the first group A O C > A C C.

A very striking change is the sudden lowering of the values after the fifth year, especially the A O C, which now becomes less than A C C. Chvostek's sign was obtained in only one of 228 children up to the fifth year. Coincident with the lowered electrical values after this age the Chvostek increases in frequency up to 25 per cent. of all children at 9 years.

Holmes finds difficulty in interpreting some of the low values found in apparently normal children. Reviewing his work, several points need emphasis: The children examined were not normal healthy children, as all were hospital patients, coming for relief of some ailment. May not some of their symptoms have been milder and obscure manifestations of spasmophilia, such as enuresis, petit mal, mild gastro-intestinal disturbances, vasomotor instability; such symptoms as constitute, according to many observers, spasmophilic diathesis? No mention is made of such symptoms existing, nor is evidence presented that their possible existence was investigated.

The study was carried on in the winter and early spring when tetany is prevalent and spasmophilia is about to become manifest. A similar study in July and August would be interesting, for there is good reason for the belief that the high percentage of Thiemich's signs that Holmes found would be lower. I shall touch on this point again.

Do such anodal reactions designate a neuropathic or spasmophilic constitution? It would be drastic to condemn as neuropaths or spasmophilics 75 per cent. of children from 6 to 7 years old. And yet these anodal reactions contrast so sharply with the reactions obtained in the other 25 per cent. at this age, where frequently only C C C is less than 5 ma., that it is difficult to let the lower values go unchallenged.

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[6] Holmes, J. B.: Reliability of Electrical Diagnosis of Tetany with Especial Consideration of the Electrical Values Found in Normal Children, Am. J. Dis. Child. **12**:1 (July) 1916.

The most recent study of spasmophilia in older children reported is that of Stheeman.[7] This observer regards Thiemich's and Escherich's signs as pathognomonic of spasmophilia. Chvostek's sign denotes first degree spasmophilia; Erb's sign denotes second degree; and the presence of both is indicative of advanced types. Of 100 children examined, Stheeman found sixty-three with "spasmophilic stigmata." The Chvostek and Erb signs occurred together in thirty-two; fourteen children had only the Erb sign and seventeen had only the Chvostek sign. The age distribution of these groups is shown in Table 2. These figures, he claims, show the frequency of the spasmophilic syndrome without tetany.

TABLE 2.—Incidence of Erb and Chvostek Signs

Age	Erb and Chvostek		Erb only		Chvostek only	
0– 3 years	9	28%	2	14%	7	44%
4– 7 years	9	28%	4	28%	8	47%
7–12 years	14	44%	8	64%	2	12%
	32		14		17	

As constitutional spasmophilic anomalies Stheeman finds: (1) digestive disturbances, deficient nutrition and other dystrophies; (2) irritability and weakness of (a) vasomotor system (angiospasm, spastic anemia etc.); (b) vegetative nervous system (vagotonia, cramps, hypermotility, atony, spastic obstipation, enuresis); (c) upper neurons (psychasthenia, neurasthenia). He found that 72 per cent. of the thirty-two children having both Erb and Chvostek's signs had digestive disturbances, and 90 per cent. had irritability and weakness of the vasomotor system. To support his contention that the electrical reactions which he designates as spasmophilic are really so, he endeavored to determine the blood calcium by means of Wright's method. This method, now obsolete, consists in drawing fresh blood into capillary tubes which contain varying strengths of an ammonium oxalate solution from fortieth to hundredth normal. The calcium is thus precipitated, and its concentration is assumed to be in direct ratio to the amount of oxalate required to prevent clotting. The method is, of course, fallacious in that it assumes calcium to be the only factor concerned in blood clotting. Normally fortieth, fiftieth and sixtieth normal solutions will prevent coagulation. With this method Stheeman found that many children showing anodal hyperirritability (Thie-

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7. Stheeman, H. A.: Spasmophilia of Older Children, Jahrb. f. Kinderh. **36**:42, 1917.

mich's sign) have blood which is prevented from clotting by ninetieth or hundredth normal ammonium oxalate solutions. However, not all such children show this and some require even stronger than fiftieth normal solution to inhibit clotting. Thus, in a table of results, twelve so-called spasmophilics require only seventieth normal or weaker solutions; nine require sixtieth or fiftieth normal, and three require fortieth normal solutions to inhibit coagulation. In another table are given results of this method applied to diseases other than spasmophilia. One case of miliary tuberculosis did not clot with eightieth normal solution; two cases of rickets and "gastro-intestinal insufficiency" did not clot with seventieth normal solution. In this same table are reported thirteen cases of so-called spasmophilia requiring sixtieth normal or stronger solutions. They are, therefore, normal in this respect.

Stheeman now concludes that as one finds in these older children with Thiemich's sign the same low blood calcium as is found in infantile tetany, the two conditions are identical. He advocates the use of the terms "spasmophilic asthenia" or "asthenia of Erb's type" to designate the anodal hyperirritability in older children.

AUTHOR'S TESTS

The electrical excitability of 146 children, ranging in ages from 2 to 7 years were tested. The tests were performed in February and March, when spasmophilia is at its peak. The children were all inmates of an institution, had no ailments of any kind, were on a liberal diet and had the usual routine allowance of play, exercise in the open air and kindergarten attendance. The technic of the tests was described in the first paper of this series.

In Table 3 are given the average values found in the different age groups, together with the number and percentage of Chvostek's and of Thiemich's signs obtained.

TABLE 3.—Average Values of Electrical Excitability at Different Ages

						A O C < A C C		Chvostek	
Age	Number Examined	C C C	A C C	A O C	C O C	Number	Per Cent.	Number	Per Cent.
2-3 years	27	1.9	4.1	4.3	>5	6	22	5	18
3-4 years	36	1.7	3.5	4.1	>5	8	22	12	33
4-5 years	53	1.9	3.6	4.3	>5	12	22	10	19
5-6 years	25	1.9	3.2	3.5	>5	10	40	9	36
6-7 years	5	1.6	3.8	3.4	>5	4	80	2	40
2-7 years	146	1.8	3.6	3.9	>5	40	27	38	26

In computing these averages one must remember that, as it is not desirable to try for a response with currents stronger than 5 ma., many of the values for the A C C and A O C, which may be very much greater than 5, are recorded only as "greater than 5" and are reckoned as 5 in the average. It is evident, therefore, that the above averages for the A C C and A O C are lower than they should be. The number of children showing no response to currents of less than 5 ma. is shown in Table 4.

TABLE 4.—CHILDREN SHOWING NO RESPONSE TO CURRENTS OF LESS THAN 5 MILLIAMPERES

Age	No. Examined	A C C > 5		A O C > 5	
2–3 years	27	12	44%	18	66%
3–4 years	36	2	5%	21	60%
4–5 years	53	9	17%	33	62%
5–6 years	25	2	8%	11	44%
6–7 years	5	2	40%	1	20%

Table 3 shows that from the second to the fifth year Thiemich's sign occurs quite regularly in 22 per cent. of the children. Between the fifth and the sixth year, 40 per cent. had such anodal reactions, while the number of children over 6 years of age is so small that the high percentage of these reactions means little. It is significant, however, that Holmes found that 75 per cent. of children at this age gave the anodal reactions of Thiemich.

As might be expected, if any pathologic significance is to be attached to Thiemich's sign in older children, girls show these reactions more frequently than boys. Of sixty-three girls tested, twenty-one, or 33 per cent. were positive; nineteen of eighty-three boys, 23 per cent., reacted in this manner. It is interesting to note that between the second and fifth years more than 60 per cent. of the children have A O C > 5.

What is the relation between Chvostek's sign and Erb's phenomenon? Holmes found only one positive Chvostek in children under 5 years. I obtained it in twenty-seven. In testing for this sign, one must be careful to tap over the nerve with sufficient force. I have repeatedly obtained a definite Chvostek with a harder tap when I had almost put it down as negative because of failure to respond to a gentle tap. Of the forty children exhibiting Thiemich's sign, fourteen (35 per cent.) had positive Chvostek's (seven boys and seven girls), while the total number of Chvostek signs obtained was thirty-eight (twenty girls, or 31 per cent. and eighteen boys, 21 per cent.). I have not found that the older children show this sign more frequently than the younger, as Stheeman records, nor do I obtain lower electrical values in those children who have both Erb and Chvostek signs. On this point I am not in agreement with Stheeman.

With the exception of enuresis, no very definite information was obtainable about such symptoms as have been described by others as constituting spasmophilia, namely, petit mal, digestive disturbances, vasomotor instability. Practically all institutional children up to 3 years wet themselves. Among children more than 3 years old, wetting occurred as follows: Of fifty-one girls, twenty-two wet themselves, and eight of these showed Thiemich's sign; of sixty-nine boys, 35 wet the bed or their clothes and eight of these exhibited Thiemich's sign. In none was a history of petit mal, breath holding spells or absences obtained. Some of the children had milder digestive upsets such as vomiting, diarrhea or constipation, but these seemed not to be related to their electrical irritability. Some were underweight, but time and again I was astonished to obtain so-called anodal hyperirritability in robust, well nourished children, exhibiting no fear of being tested and in no way neurotic or of the "cry-baby" type.

It was stated above that a study of this kind carried out in the summer months would be interesting by comparison with a study in the season when spasmophilia and tetany are at their height. A repetition of this work is now being planned for August.

SUMMARY

1. The work of Holmes and of Stheeman on the electrical reactions and their significance in older children is reviewed.

2. Electrical tests were performed on 146 healthy children between the ages of 2 and 7 years, living in a modern child-caring institution.

3. The average values found in these children are: C C C, 1.8; A C C, 3.6; A O C, 3.9; C O C, > 5.

4. Thiemich's sign occurred in forty instances, or 27 per cent.

5. Chvostek's sign was obtained in thirty-eight cases, fourteen of which, or 35 per cent., also manifested Thiemich's sign.

6. Enuresis occurred often, but only a small percentage of these children had Thiemich's sign.

7. Over 60 per cent. of 116 children between the ages of 2 and 5 years have an A O C > 5, while over 20 per cent. at these ages show A O C $<$ A C C and < 5.

8. The incidence of Thiemich's sign is somewhat higher in girls than in boys.

9. In no case was Escherich's sign (C O C < 5) obtained.

CONCLUSIONS

I heartily agree with those who state that it is difficult to interpret the electrical reactions of older children. In general, in view of the increasing frequency with which so-called anodal hyperexcitability reactions are obtained as the child grows older, it is safe to assume that those are the reactions one may expect to find and they should not, therefore, constitute a diagnosis of spasmophilia in the entire absence of all clinical symptoms.

Thiemich's sign in older children does not necessarily point to a neurotic or spasmophilic constitution.

The writer wishes to acknowledge his gratitude to Dr. Alfred F. Hess of New York for many privileges granted in carrying out this study.

EMPYEMA IN INFANTS AND YOUNG CHILDREN *

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In reviewing the literature on empyema in infants and young children, it was found that the number of extensive articles on this subject was surprisingly few. Since the majority of admissions to the Babies' Hospital are children under 3 years of age, an exceptional field is offered to observe this disease in the very young. For this reason it seemed worth while to make a study of the cases which have been treated during the last seven years. The cases treated prior to this time were analyzed in 1913 by Holt.[1]

From Jan. 1, 1913 to Jan. 1, 1920, 204 cases of clinical empyema were treated at the Babies' Hospital. Of this number 113 babies recovered and 91 died, a mortality of 44.6 per cent. Cases are classed as empyema in which pus or cloudy serum was obtained from the pleural cavity by exploratory punctures. From this pus or seropus bacteria were always grown. In six instances only a few cubic centimeters of cloudy serum were obtained, the infant recovering after puncture without the accumulation of more exudate in the pleural cavity. Cases of this type, from which bacteria were cultivated from the exudate, are included as examples of empyema.

INCIDENCE

The combined cases of pneumonia and empyema, which were admitted to the hospital during the period in which this series of cases was studied, numbered 1,869. Approximately, then, 11 per cent. of all the pneumonia patients either had an empyema at the time of admission or developed it in the hospital. This incidence of one empyema to nine pneumonias corresponds very closely to that of Dunlop,[2] who in a study of ninety-eight children with empyema found the frequency to be one empyema to every eight or nine pneumonias. Churchill,[3] on the contrary, states that this complication is relatively infrequent in children, empyema occurring once in every twenty cases of pneumonia.

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* From the records of the Babies' Hospital, New York.

[1] Holt, L. E.: The Siphon Treatment of Empyema in Infants and Young Children Compared With Other Measures: A Study of 154 Cases, Am. Med. **8**:381 (June) 1913.

[2] Dunlop, H. G. M.: Empyema in Children, Edinburgh M. J. **13**:1, 1914.

[3] Churchill, F. S.: Empyema in Children with Special Reference to Diagnosis, Boston M. & S. J. **181**:87 (July 24) 1919.

The mortality by ages is given in Table 1.

TABLE 1.—AGE AND MORTALITY

Months	Total Cases	Recovered	Died	Mortality, per Cent.
0- 3	3	1	2	66.7
3- 6	17	4	13	76.5
6-12	33	14	19	57.6
12-24	85	42	43	50.6
26-36	37	27	10	27.0
Over 3 years	29	25	4	13.8

This table shows that the age of the infant is perhaps the largest single factor concerned in determining the prognosis. Among the twenty patients under 6 months of age, the mortality was 75 per cent.; among the fifty-three infants under 1 year, the mortality was 64 per cent., while for the twenty-nine over 3 years of age, the mortality was only 13.8 per cent.

The youngest case in this series was an infant only 22 days old. He was a male child admitted when fourteen days old with diarrhea of two days duration. The admission weight was 7 pounds. The physical examination revealed a definite pulmonary consolidation at the right base. Eight days after admission the physical signs at the right base were suggestive of fluid. An exploratory aspiration was done and pus was obtained. Continuous drainage by the syphon method was instituted under local anesthesia. The tube remained in the chest for sixteen days. Three days after its removal the baby was discharged in good condition. The temperature ranged between 99 F. and 103 F. before operation. It became normal the day after operation and remained so until discharge. Two blood cultures gave negative results. The white blood count was 44,000; polymorphonuclears 84 per cent., lymphocytes 16 per cent., the day after admission. The organism found was *Staphylococcus aureus* in pure culture. The baby was breast fed while in the hospital, and weighed 6½ pounds on the day of discharge. An observation four months afterward showed that he was thriving satisfactorily.

There were four cases of recovery in infants between 3 and 6 months of age. Pneumococcus was the organism found in the pus from the pleural cavity in three cases, staphylococcus in one. Siphon drainage was the treatment employed in three of these, and the tube remained in the chest nine, fifteen and sixteen days respectively. In the fourth case, an infant 5 months old, two aspirations were done and a total of 9 c.c. of seropus containing many pneumococci was obtained. This patient recovered without the removal of any more fluid from the pleural cavity.

SEX

There were 124 boys and 80 girls in this series. That the disease is so much more frequent in males than in females is rather surprising. The difference in this series is, however, not so marked as in the series of 154 cases reported by Holt,[1] in which 104 cases occurred in male infants and only 50 cases in females. The mortality for the males was 43.6 per cent., while that for the females was 46.3 per cent.

TABLE 2.—Conditions Associated With Empyema

	Cases	Recovered	Died
Primary pneumonia	168	102	66
Pneumonia complicating measles	12	5	7
Pneumonia complicating whooping cough	4	2	2
Pneumonia complicating diphtheria	1	0	1
Pneumonia complicating varicella	1	0	1
Pneumonia complicating gastro-enteritis	9	3	6
Pneumonia complicating miliary tuberculosis	4	0	4
Pneumonia complicating retropharyngeal abscess	1	0	1
Pneumonia complicating tonsil and adenoid operation	2	1	1
Pneumonia complicating syphilis	2	0	2

Pneumonia was present in every case of this series. In 168 instances the pneumonia was primary and uncomplicated. Of these infants 102 recovered and 66 died, a mortality of 39 per cent. These cases are interesting when compared with those in which the pneumonia occurred as a complication of the common contagious diseases of childhood. In this group there were eighteen cases with eleven deaths, a mortality of 61 per cent. Contagious diseases are not admitted to the Babies' Hospital. This group is, therefore, very small. The high mortality is even more significant when the ages of these children are taken into consideration. The mortality for the twelve measles cases was 59 per cent. None of these children was under 1 year of age; eight of them were between 1 and 2 years old, and four were between 2 and 3 years old. The mortality for the children of this age in the entire series was 43 per cent.

DURATION OF SYMPTOMS BEFORE OPERATION

It is a general opinion that the duration of symptoms before operation is a matter of much importance in prognosis. The influence of the duration of the symptoms before the operation on the mortality of the 168 cases of empyema complicating primary pneumonia is shown in Table 3.

In three of these cases the duration of the respiratory symptoms was less than one week before operation. Such a rapid development of empyema to the point where operation is needed is not common. Details of these three cases are of considerable interest.

TABLE 3.—Empyema Following Primary Pneumonia, Duration of Symptoms and Results

Duration of Symptoms	Cases	Recovered	Died	Mortality, per Cent.
0–1 week	3	1	2	67
1–2 weeks	36	17	19	53
2–4 years	80	51	29	36
4–6 weeks	30	23	7	23
6 weeks and over	19	10	9	47

REPORT OF CASES

Case 1.—A male infant, aged 16 months, was admitted because of cough and fever for two days. The physical examination was suggestive of fluid in the right pleural cavity. An aspiration was done on the day of admission and 300 c.c. of pus was removed. Six days later 300 c.c. of pus was removed by a second aspiration. Eight days after admission siphon drainage was employed. The temperature became normal the second day after operation and the patient recovered. A culture of the pus from the chest showed a pure growth of pneumococci.

Case 2.—A male infant, 3 months old, was admitted because of irritability and fever for one day. The physical signs of the left chest suggested fluid. Pus was obtained by an exploratory puncture the day after admission, and siphon drainage was employed. The infant died thirteen days after operation. The blood culture was sterile. The pus from the pleural cavity contained streptococci. The necropsy showed acute bronchopneumonia with fibrinopurulent pleurisy over both lobes of the left lung.

Case 3.—A male infant, 4 months old, was admitted with a history of diarrhea for four days. Physical signs were typical of fluid in right chest posteriorly. Pus was obtained by an exploratory puncture two days after admission, and siphon drainage was employed. The infant died two days after operation. The pus from the chest contained streptococci. Necropsy showed fibrinopurulent peritonitis, fibrinopurulent pericarditis and extensive bronchopneumonia with fibrinopurulent pleurisy over the whole right lung. Streptococci were found in the culture of all these exudates.

In view of the fact that bronchopneumonia was present in the lung of the affected side in both cases which came to necropsy, the conclusion seems warranted that in none of these cases was the empyema primary. Every case of empyema in this hospital which has come to necropsy, showed the empyema to be secondary to pneumonia.

It is interesting to note in Table 3 that in those cases in which the symptoms had lasted less than six weeks before operation the mortality decreased with the duration of symptoms. In nineteen cases in which the symptoms had lasted six weeks or more before operation there was a mortality of 47 per cent. This is high when compared to a mortality of 23 per cent. in the thirty cases in which symptoms had lasted from four to six weeks before operation.

The high mortality of the cases in which symptoms were of short duration before the operation is undoubtedly due chiefly to the greater intensity of the infection. The high mortality in the cases in which operation was done late may be due to complications which interfere with expansion of the lung, chronic thickening of the pleura and pericardium, carnification of the lung, etc. The lowest mortality is seen in the middle group of cases. Early cases include those of greatest severity, and very late cases include the neglected ones.

LOCATION OF THE DISEASE

The left side of the chest was involved in 109 cases; the right in 91 cases; both sides were affected four times. These four cases of double empyema present some points of interest. Three of the cases were fatal. Two patients were treated by aspiration and one patient was treated by siphon drainage. In the patient who recovered the disease did not develop on the two sides simultaneously. Siphon drainage was the treatment employed, and the operations were twenty days apart.

PHYSICAL SIGNS

The most important physical signs of fluid in the pleural cavity of the young child are flatness on percussion, and displacement of the heart. It is a rule in the Babies' Hospital to do an exploratory puncture in every acute respiratory condition in which flatness to percussion is present. Of course, only by puncture can purulent and serous exudations be distinguished. Displacement of the heart is of great importance in diagnosis when present. But when the amount of pus present is small, and in a large number of the cases in young children the empyema is localized, the displacement is slight or absent altogether. This sign was absent in more than one third of the cases studied. Bronchial breathing is more often present than absent and while it is usually feeble and nasal in quality, it is very often indistinguishable from that which is heard over consolidation of the lung.

The type of infection has considerable influence on the mortality of this condition, as shown in Table 4.

TABLE 4.—BACTERIOLOGY AND MORTALITY

	Cases	Recovered	Died	Mortality, per Cent.
Pneumococcus alone	142	82	60	42
Staphylococcus alone	32	18	14	44
Streptococcus alone	20	9	11	55
Bacillus of Pfeiffer alone	2	1	1	50
Mixed Infections				
Streptococcus and pneumococcus	2	1	1	50
Pneumococcus and bacillus of Pfeiffer	5	1	4	80
Staphylococcus and bacillus of Pfeiffer	1	1	0	0

The pneumococcus was present in pure culture in 70 per cent. of the cases; and this group shows the lowest mortality in the series. The highest mortality, 62 per cent., was among the cases (eight) of mixed infection. The streptococcus cases showed the highest mortality of the single infections. There were twenty of these and their mortality was 55 per cent.

Holt [1] found that the staphylococcus infections were more frequent in the very young infants. The age and the type of infection in this series are given in Table 5.

TABLE 5.—AGE AND TYPE OF INFECTION

	First Year		Second Year		Third Year		Over Three Years	
	Cases	Died	Cases	Died	Cases	Died	Cases	Died
Pneumococcus......	31	20	61	32	25	7	25	1
Staphylococcus.....	10	5	17	8	4	1	1	0
Streptococcus.......	9	7	3	1	6	1	2	2
Bacillus of Pfeiffer.	1	0	..	..	1	1		
Mixed infections....	2	2	4	2	1	0	1	1

This series of cases also shows a greater frequency of staphylococcus infections in the first and second years. Streptococcus infections are also more frequent during the first two years of life. Tubercle bacilli were not found in the pus in any instance, but general miliary tuberculosis was found at necropsy in four cases; the empyema, however, was non-tuberculous.

BLOOD EXAMINATION

A leukocyte count, together with the differential count, was made before operation in all but five cases.

The average count in cases ending in recovery was:

82 pneumococcus cases	31,900
18 staphylococcus cases	32,800
9 streptococcus cases	30,500
3 mixed infection cases.................................	45,000

The average count in the fatal cases was:

58 pneumococcus cases	31,700
12 staphylococcus cases	37,500
10 streptococcus cases	44,000
5 mixed infection cases.................................	23,000

Two cases with unusually low leukocyte counts are especially interesting. Both terminated fatally. One, a child of 3 years, had a leukocyte count of 7,200. The organisms present in the pus from the chest were pneumococcus and Bacillus of Pfeiffer. The case was complicated by a pneumococcus septicemia, pneumococcus pericarditis and miliary tuberculosis. In the other case, a child of 10 months, the leukocyte count was 9,800. A pure culture of pneumococci was grown from the pus obtained from the pleural cavity. Otitis media and ulcerative colitis were complications. The highest leukocyte count in the series was 83,000. This was seen in an infant 1 year old, who died the day after operation. Pneumococcus was present in the pus from the chest. This case was complicated by a pneumococcus septicemia with pneumococcus meningitis.

It is evident that no conclusion as to prognosis can be drawn from the leukocyte count. The leukocyte count is also of little value in making the diagnosis between empyema and pneumonia. In many instances the empyema developed in patients under observation without any noticeable increase in the leukocytosis.

Blood cultures were made in 115 of the cases studied, of which 43 were positive and 72 were negative. This type of infection, and the mortality are shown in Table 6.

TABLE 6.—Prognostic Value of Blood Cultures

	Negative Cases	Died	Positive Cases	Died
Pneumococcus alone........................	51	18	34	20
Streptococcus alone.........................	9	6	2	2
Staphylococcus alone.......................	10	4	4	3
Bacillus of Pfeiffer alone....................	1	0	1	1
Mixed infections............................	1	1	2	2

It is to be noted that fifteen of the infants with general blood infection recovered. The blood culture of fourteen of these showed pneumococci; of one, staphylococci. The majority of these blood infections were found in cases in which there was a rapid general infection, and in which the empyema developed as a complication in the earlier stages of the pneumonia.

TABLE 7.—Results With Different Methods of Treatment

Type of Treatment	Cases	Recovered	Died	Mortality, per Cent.
Siphon drainage..............................	142	86	56	39.4
Simple incision and drainage................	29	14	15	51.7
Rib resection..................................	9	5	4	44.4
Aspiration.....................................	24	8	16	66.6

The majority of these cases, it will be seen, were treated by siphon drainage. This method of treatment has been described by Holt.[1] Simple incision between the ribs and the introduction of one or two short rubber tubes was the treatment employed in twenty-nine cases. Rib resection was the primary operation in only nine of these children. In twenty-four the only treatment was aspiration; the number of aspirations done on a single patient varied from one to six. Aspiration was the method of treatment used only in those infants who were so acutely ill that it seemed unwise to do a more serious operation. The mortality, 66.6 per cent., in this group is for this reason very high. In two of these cases (ages 7 and 13 months, respectively) 300 c.c. of pus were removed from the pleural cavity by three and four aspirations, respectively. Both these children recovered without other surgical interference. Pneumococcus was present in the pus from the chest of the younger, streptococcus in that from the chest of the older infant.

Dr. Homer F. Swift[4] in a study of pneumococcus empyema in adults, advises early operation as soon as the diagnosis has been made. In his experience all cases in which a pleural exudate containing bacteria was obtained, ultimately came to operation. This has not been the experience with infants and young children at the Babies' Hospital. In six cases a seropurulent exudate varying in amounts from a few drops to 15 c.c., and containing many pneumococci, was obtained by aspiration of the pleural cavity. These six patients recovered without any further removal of fluid.

TABLE 8.—Age and Results by Different Methods of Treatment

Age	Siphon Drainage		Simple Incision with Drainage		Aspiration		Rib Resection	
	Cases	Died	Cases	Died	Cases	Died	Cases	Died
First year..........	36	20	8	7	9	7		
Second year..........	59	27	9	4	12	8	5	4
Third year..........	31	9	3	1	2	0	1	0
Over 3 years..........	16	0	9	3	1	1	3	0

It is to be noted in Table 8 that rib resection was not done on any infant under 1 year old. Yet the mortality for the nine children so treated is 44 per cent. Among those cases treated by siphon drainage and those by simple incision with drainage, the method chosen was not determined by the age; neither were certain types of cases, as mild or severe, chosen for the different methods of treatment.

The mortality of 39.4 per cent. in cases treated by syphon drainage is the lowest in the series. The best results with syphon drainage were obtained when this could be maintained without interruption as long as a week. The average number of days in which syphon drainage was maintained for the 86 cases who were treated by this method, and who recovered, was 6.4 days. In only fourteen of the fatal cases so treated was siphon drainage maintained six days or longer; and in all of these the fatal outcome was greatly influenced by complications. Siphon drainage has to be discontinued occasionally for one of two reasons: First, plugging of tube by masses of fibrin; second, air leakage around the tube due to faulty technic during operation or to ulceration around the tube.

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[4] Swift, H. F.: The Treatment of Empyema Caused by Pneumococci. Read before the New York Academy of Medicine, March 16, 1920.

One of the greatest difficulties in the way of the recovery of young infants with empyema is imperfect pulmonary expansion due to the soft thoracic wall and to feeble respiratory muscles. Treatment by siphon drainage favors early and easy expansion. Cotton[5] believes that the proper utilization of the knowledge of pneumodynamics in the treatment of empyema in children will lower the mortality, decrease the number of chronic cases, and furnish adequate means of treating chronic cases without frequent resort to the radical and deforming operations of the past. The superiority of siphon drainage over any other method of treatment of empyema in early infancy used in this hospital has been clearly demonstrated, and the observations of Cotton seem justifiable. The observations of Kelly,[6] on the other hand, are hardly warranted when he says that "pumps, siphons, valves and suction apparatus are more bother than they are worth in children."

COMPLICATIONS

Table 9 shows how frequent complications are with empyema, and that death is often due to causes not connected with the pulmonary condition.

TABLE 9.—Complications

	Recovered	Died
Otitis media	33	24
Pneumonia in opposite lung	4	22
Gastro-enteritis	12	25
Diphtheria	1	6
Erysipelas	1	3
Acute nephritis	1	2
Bacillary dysentery	1	
Miliary tuberculosis	..	4
Ulcerative colitis	..	2
Congenital heart disease	..	1
Peritonitis	..	3
Retropharyngeal abscess	..	1
Congenital syphilis	..	2
Osteomyelitis of rib	..	1
Measles	..	1
Meningitis (pneumococcus)	..	2
Meningitis (streptococcus	..	1
Meningitis (tuberculosis)	..	1
Pyelitis	..	4
No complications	40	4

Of the infants who died, four had definite miliary tuberculosis, three had peritonitis (the organism in each case was the same as that present in the pus from the chest), two, age 3 months each, had congenital syphilis, and four had meningitis. The complications in thirteen of these infants, therefore, were of such severity that there was little hope for their recovery whatever the treatment employed. The most interesting observation in Table 9 is the fact that among the fatal cases there were only four who did not present some serious lesion besides the pulmonary condition.

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[5] Cotton, F. J.: Pneumodynamics of Empyema, Boston M. & S. J. **173**:800, 1915.

[6] Kelley, S. W.: Drainage of Acute Pleural Empyema in Children, Am. J. Surg. **26**:47, 1912.

POSTMORTEM OBSERVATIONS

Necropsies were performed in sixty-four of the ninety-one fatal cases. These cases, grouped according to the anatomic diagnosis, are shown in Table 10. Lobar pneumonia was found in only three, while bronchopneumonia was present in fifty-five. This, of course, is due to the fact that bronchopneumonia is much more frequent during the first two years of life. It is interesting to note that Dunlop[2] states that empyema followed lobar pneumonia in 69 per cent of a series of ninety-eight cases studied by him. His series includes a much larger number of older children than does this series of cases.

TABLE 10.—Necropsy Findings in Sixty-four Fatal Cases

	Cases
Bronchopneumonia	55
Lobar pneumonia	3
Carnification of the lung	10
Multiple pulmonary abscesses	8
Pseudomembranous pleurisy (Klebs-Loeffler origin)	1
Diphtheritic laryngitis	2
External pericarditis	20
Internal pericarditis	2
Miliary tuberculosis	4
Purulent peritonitis	8
Acute colitis	7
Purulent arthritis	1

Practically all cases coming to necropsy showed a fibrinopurulent pleurisy varying from a small amount of thin fibrin shreds to an extensive fibrinopurulent exudate, from 1 to 2 mm. in thickness; the lesion was double in nine cases. External pericarditis was found in twenty cases. This was more frequently found in those cases in which the left side was involved. Purulent peritonitis was present in eight cases; in five, this condition had not been recognized during life.

There was only one case of empyema necessitatis, or external opening through the thoracic wall in this series; and in no instance was there a rupture of the pus into a large bronchus or into the esophagus; nor did the pus burrow behind the diaphragm, causing a psoas or subdiaphragmatic abscess. Localized empyema was frequent. The pus cavity was localized in the majority of cases which came to necropsy; but in no instance was interlobar empyema seen either at necropsy or at operation.

DURATION OF LIFE AFTER OPERATION IN FATAL CASES

Of the fatal cases treated by siphon drainage, twenty-three patients died within the first week, while twenty lived twelve days or longer after operation. All of the patients on whom rib resection was done lived longer than twelve days; and five of the cases treated by simple incision with drainage lived twelve days or longer. In nearly one third of these cases, then, the death was probably from exhaustion due to prolonged sepsis and to imperfect expansion of the affected lung. These patients died in spite of the fact that in every instance the drainage was perfect.

TIME OF OPERATION

It is the experience of the Babies' Hospital, unless the accumulation of fluid in the pleural cavity is very rapid, that the infant's chances of recovery are improved by delaying the operation until the acute inflammatory process in the lung itself has subsided. In some of these cases aspiration may be done for temporary relief, the opening of the chest being deferred.

CONCLUSIONS

1. The mortality of empyema in infants and very young children is high with all methods of treatment employed.
2. Approximately 11 per cent. of all the cases of pneumonia admitted to the Babies' Hospital during the last seven years either had empyema at the time of admission or developed it during the stay in the hospital.
3. The mortality in empyema decreases very rapidly as the age of the infant advances.
4. Empyema was the sequel of pneumonia in every case of this series. When pneumonia is a complication of the common infectious diseases of childhood the mortality is very high.
5. Pneumococcus in pure culture was present in the pus from the pleural cavity in 70 per cent. of these cases; the mortality for this type of infection is the lowest in the series.
6. The degree of leukocytosis is no guide to prognosis or to diagnosis.
7. In the experience of the Babies' Hospital siphon drainage has given better results in the treatment of empyema in infancy than any other method of treatment employed.

The writer wishes to express thanks to Dr. L. Emmett Holt for permission to use the hospital records in making this report and for his assistance in its preparation.

A STUDY OF THE URINE SUGAR IN INFANTS*

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It has long been considered probable that the urine of normal individuals contains a reducing sugar. Benedict, Osterberg and Neuwirth[1] recently demonstrated the constant presence of sugar in normal urine and devised a method for its quantitative determination. They found that the amount of sugar in the urine was directly influenced by the quantity of sugar ingested. They also demonstrated that the urine sugar can be separated into two fractions by fermentation with yeast, a fermentable and a non-fermentable portion.[2]

During the course of work in this laboratory on the sugar tolerance of infants, a number of determinations of urine sugar have been made. These determinations have led to observations which seem of sufficient interest to report.

Technic.—The infants on whom observations were conducted were all practically normal in the sense of being free from infections or gastro-enteric disturbances. Many were of normal weight, a few were underweight for their age. All of the patients were under 7 months of age. If at any time an infant became ill, observations were discontinued until after complete recovery. Most of the infants were on four hour feeding intervals and received six feedings daily. The urine was usually collected over a period of eight hours. Each separate voiding was immmediately transferred to a bottle kept on ice and as a further precaution toluene was added as a preservative. The analyses of the urines were made as soon after collection as possible. These precautions are necessary, as much of the sugar present in the urine is very easily lost by fermentation when kept in a warm room. The determinations were made according to the method of Benedict and Osterberg with a few slight modifications. In order to insure complete precipitation of all reducing substances other than sugar, urines with a specific gravity of more than 1.010 were diluted with sufficient water to reduce the specific gravity to that point. The mercuric nitrate reagent was diluted with water in the proportion of seven parts of the reagent to three parts of water. In producing the color reaction, the tubes were immersed in boiling water for twenty minutes [3] instead of ten minutes.

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[1] Benedict and Osterberg: J. Biol. Chem. **24**:195, 1918. Benedict, Osterberg and Neuwirth: J. Biol. Chem. **24**:217, 1918.

[2] Throughout this report, the reducing substance in urine which is not fermented by yeast will be referred to as non-fermentable sugar. The exact nature of this substance is unknown at present.

In all specimens the total sugar was determined and also the non-fermentable portion was determined by fermenting the urine with yeast for from 18 to 24 hours. The fermentable portion was derived by subtraction.

The twenty-four hour sugar excretion was calculated on the basis of the period of observation. Each specimen of urine was tested with Benedict's qualitative reagent.

At the beginning of the observations, the baby was usually placed on a formula consisting of 1½ ounces of milk per pound of body weight in order to fulfil the fat and protein requirements. Sugar was added in moderate amount and then gradually increased at from three to four day intervals, leaving the rest of the formula constant. In this way the relation of the amount of sugar secreted in the urine to the amount of sugar ingested was studied. In some cases the sugar was first increased and then reduced in order to ascertain further the relation of the sugar in the food to the urine sugar. Frequent analyses of the urine sugar were made on other infants whose formula was unchanged. This was to determine the sugar excretion, both fermentable and non-fermentable on the basis of a constant sugar intake.

AMOUNT OF SUGAR IN INFANT'S URINE

One hundred and seventy urine sugar determinations were made on 37 infants. Considering all cases, the calculated twenty-four hour total sugar excretion varied from 100 to 815 mg. The non-fermentable portion varied from 45 to 253 mg. Similar to the work of Benedict, Osterberg and Neuwirth on adults, our results show that the amount of urine sugar in infants is dependent to a considerable degree on the amount of sugar ingested. For this reason, the larger values obtained by us do not indicate the normal sugar excretion, as in many cases the infants received much larger amounts of sugar than are usually fed. Considering only the amount of urine sugar in infants receiving from 6 to 7.5 per cent. sugar, the values for total sugar range from 100 to 400 mg., and for the non-fermentable portion from 45 to 150 mg. Benedict, Osterberg and Neuwirth found that adults excrete from 600 to 1,200 mg. of total sugar on an ordinary diet. The nonfermentable portion varied from 340 to 660 mg. As would be expected, infants excrete a smaller absolute amount of sugar, but the amount in proportion to body weight is much greater.

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[3] These modifications were made at the suggestion of Dr. Benedict (personal communication to Dr. Schloss).

It was found that the quantity of sugar excreted is quite independent of the volume of urine. For example, one infant, A. H., excreted 65 c.c. of urine containing 63 mg. of sugar during one period. At another time he excreted only 28 c.c. of urine during a period of equal length, but this specimen contained 76 mg. of sugar. The first urine contained 97 mg. of sugar per hundred c.c., while the second contained 228 mg. per hundred c.c.

TABLE 1.—Showing Effect on Urine Sugar of Feeding Increasing Amounts of Sugar. A. G., Aged 4 Months. Collection Period 8 Hours: 8 a. m. to 4 p. m.

Date	Urine, C.c.	Total Urine Sugar		Nonfermentable Sugar			Fermentable, Sugar, Mg.	Weight, Pounds and Ounces		Formula	Benedict's Qualitative Test
		Per Cent.	Mg.	Per Cent.	Mg.	Per Cent. of Total Sugar		Lb.	Oz.		
2/ 5	95	0.056	52.9	0.031	29.5	57	23.4	11	5	Milk, 20 oz. Lactose, 1 oz. Barley water to 30 oz. 6 × 5 oz.	0
2/16	125	0.047	58.6	0.017	21.8	38	26.8	11	11	Milk, 22 oz. Lactose, 1½ oz. Barley water to 30 oz. 6 × 5 oz.	0
2/28	70	0.167	116.6	0.040	27.2	24	93.2	12	4	Milk, 22 oz. Lactose, 2½ oz. Barley water to 30 oz. 6 × 5 oz.	+
3/ 5	80	0.158	130.1	0.035	28.4	22	101.7	12	8	Milk, 22 oz. Lactose, 3½ oz. Barley water to 30 oz. 6 × 5 oz.	+
3/10	75	0.186	139.8	0.039	29.4	20	110.4	13	4	Milk, 22 oz. Lactose, 4 oz. Barley water to 30 oz. 6 × 5 oz.	+

Relation of Sugar Intake to Sugar in Urine.—It has been mentioned that the excretion of sugar in the urine is directly dependent on the amount of sugar ingested. This was found to be true of all the cases studied. An example of a typical case is given in Table 1. It will be seen that as the sugar in the formula was increased, the total urine sugar was also increased. The increased excretion of sugar was confined chiefly to the fermentable portion. It is also to be noted that as the total urine sugar increased the percentage of nonfermentable sugar became less. On the first formula the nonfermentable sugar was 57 per cent. of the total and on the last formula, which contained the greatest amount of sugar, the nonfermentable portion dropped to 20 per cent. of the total. The total urine sugar excreted on the last formula was nearly three times as great as on the first formula.

TABLE 2.—Showing Sugar Excretion in Urine When Sugar Was First Increased and Then Decreased. R. H., Aged 5 Weeks.
Collection Period 8 Hours: 8 a. m. to 4. p. m.

Date	Urine, C.c.	Total Urine Sugar		Nonfermentable Sugar			Fermentable, Sugar, Mg.	Weight, Pounds and Ounces		Formula	Benedict's Qualitative Test
		Per Cent.	Mg.	Per Cent.	Mg.	Per Cent. of Total Sugar		Lb.	Oz.		
4/ 9	68	0.099	59.6	0.031	21.6	36	38.0	9	4	Milk, 13 oz. Dextri-maltose, 1 oz. Barley water to 24 oz. 6 × 4 oz.	+
4/16	57	0.136	75.7	0.047	26.8	35	48.9	9		Milk, 14 oz. Dextri-maltose, 1½ oz. Barley water to 24 oz. 6 × 4 oz.	+
4/21	55	0.213	116.9	0.064	35.0	30	81.9	9	8	Milk, 14 oz. Dextri-maltose, 2 oz. Barley water to 24 oz. 6 × 4 oz.	+
4/29	53	0.251	132.6	0.059	31.5	23	101.1	9	10	Milk, 14 oz. Dextri-maltose, 2½ oz. Barley water to 24 oz. 6 × 4 oz.	+
5/11	27	0.179	48.3	0.085	22.9	47	25.4	8	15	Milk, 12 oz. Dextri-maltose, 1 oz. Barley water to 24 oz. 6 × 4 oz.	+
5/17	81	0.106	86.1	0.042	33.9	40	52.2	8	14	Milk, 12 oz. Dextri-maltose, 1½ oz. Barley water to 24 oz. 6 × 4 oz.	+

In Table 2 are given the results of increasing the ingested sugar and then decreasing it. The rise and fall of the sugar excretion in the urine is clearly shown. The loss of weight between April 29 and May 11 was due to an intercurrent infection (rhinopharyngitis) during which time the patient was on a low formula and no determinations were made. The determination on May 11 was made one week after recovery as the sugar was being gradually increased again. It will also be noted that on two occasions during the observations (April 16 and May 17) the formula was practically the same. The sugar excretion, total, fermentable and nonfermentable, was practically constant. The collection periods were both of eight hours' duration but the amount of urine excreted was nearly 50 per cent. greater on May 17 than on April 16. This shows again that the amount of sugar in the urine is quite independent of the volume of urine.

In Table 3 the sugar excretion on a given formula is shown. It will be seen that the amount of sugar excreted remained practically constant. In adults this was also found to be true by Benedict, Osterberg and Neuwirth.

In this series of 170 determinations, a positive reaction with Benedict's qualitative sugar reagent was obtained in seventy-one. As a rule, the test was positive when the urine contained approximately 0.1 per cent. or more of sugar.

TABLE 3.—SHOWING URINE SUGAR EXCRETION WITH CONSTANT SUGAR INTAKE. C. N., AGED 2 MONTHS. FORMULA: MILK, 12 OUNCES; DEXTRI-MALTOSE, 1¾ OUNCES; BARLEY WATER TO 24½ OUNCES; 7 × 3½ OUNCES. COLLECTION PERIOD 6 HOURS: 8 A. M. TO 2 P. M.

Date	Urine, C.c.	Total Urine Sugar		Nonfermentable Sugar			Fermentable Sugar, Mg.	Weight	
		Per Cent.	Mg.	Per Cent.	Mg.	Per Cent. of Tatal Sugar		Lb.	Oz.
11/29	55	0.092	50.8	0.037	19.3	38	31.5	8	5
12/ 2	80	0.068	54.6	0.032	25.8	47	28.8	8	6
12/ 5	80	0.055	44.0	0.023	18.0	41	26.0	8	8
12/ 8	130	0.045	58.2	0.022	29.0	49	29.0	8	8

Our results lead to conclusions quite opposed to those of Porter and Dunn.[4] They examined the urines of infants who received large amounts of sugar in their food and concluded that there was no direct relationship between the amount of sugar ingested and the presence of sugar in the urine. The difference between their results and ours is probably due in part to the fact that they used a purely qualitative test for sugar and did not estimate the total sugar output. A qualitative test is positive only when the urine contains sugar in a definite concentration and is in no way indicative of the actual sugar output.

For example, 100 c.c. of urine containing 0.1 gm. of sugar would probably give a positive reaction with a copper reduction test, while 0.15 gm. of sugar in 200 c.c. of urine, which represents a larger output of sugar, would probably not reduce a copper test solution owing to the lower sugar concentration. F. H., receiving a moderate amount of sugar, excreted 40 c.c. of urine in eight hours containing 53 mg. sugar. The urine contained 0.33 gm. of sugar per 100 c.c., and Benedict's qualitative reagent was reduced. J. T., receiving a large amount of sugar, excreted 255 c.c. of urine in eight hours containing 147 mg. sugar. The sugar concentration of this urine was only 0.058 gm. per hundred c.c., and Benedict's test was negative.

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[4] Porter and Dunn: Am. J. Dis. Child. **10**:77 (July) 1915. Dunn: Pediatrics, Ed. 1 **2**:475.

Porter and Dunn make no mention of what length of time elapsed between the collection and examination of the urine specimens. It has been our experience that the amount of sugar will diminish very rapidly unless the specimen is very carefully preserved.

As mentioned previously, based on a quantitative determination of the urine sugar, our results show definitely that with increased ingestion of sugar there is an increased elimination of sugar in the urine. Based on a qualitative test alone, the greater number of positive reactions occurred when large amounts of sugar were given but positive reactions also occurred when moderate or small amounts of sugar were fed. In such instances, the urine was concentrated.

On the basis of these results, it seems that the quantitative determination of the urine sugar may prove of distinct value in estimating sugar tolerance. Its use in this connection will be the subject of a separate report.

CONCLUSIONS

1. The urine of all normal infants contains a determinable amount of reducing sugar.

2. The amount of sugar excreted is not dependent on the volume of urine but is directly proportional to the amount of sugar ingested. As the amount of sugar in the diet is increased, the total urine sugar increases. This increase is chiefly in the fermentable portion and as a result the percentage of nonfermentable sugar becomes less.

3. Sugar excretion in infants, both fermentable and nonfermentable, is fairly constant when the intake of sugar is constant.

I desire to express my appreciation to Dr. Oscar M. Schloss, at whose suggestion the problem was undertaken, for his kind criticism and advice during this study. I also desire to acknowledge my indebtedness to Miss Elizabeth S. Morris, nurse in charge of the children's wards, for invaluable aid in supervising the patients on whom observations were conducted.

BOOK REVIEW

PROPHYLAXIS AND THERAPY OF CHILDREN'S DISEASES. By PROF. F. GÖPPERT (Göttingen) and PROF. L. LANGSTEIN (Berlin). Cloth. Price, 42 marks (plus). Pp. 606, with 37 illustrations. Berlin: Julius Springer, 1920.

This is a new textbook on children's diseases by two of Germany's foremost pediatricians. Infant feeding and infant care in health and disease receive careful attention. As the volume is intended for the practitioner, therapy receives much attention. The chapter on "medicinal therapy" is rather extensive, including prescriptions containing rather obsolete vegetable derivatives as well as rather extensive lists of modern German pharmaceuticals; e. g., under urinary antiseptics there are included: cystopurin, hippol, myramalid, amphotropin, etc. The authors claim to have seen no benefit from tonsillectomy in cases of chronic arthritis nor do they think that bathing eczema cases with water a few times a week acts harmfully. Their antisyphilitic treatment is very good. The paucity of illustrations is the shortcoming of the volume. The one showing longitudinal sinus puncture for obtaining blood and that of injection into the temporal vein are good.

CORRECTION

In the paper by Milo K. Miller and Karl M. Nelson, "Elephantiasis Congenita Angiomatosa (Unna), Associated with Changes in the Capillaries," published in the AMERICAN JOURNAL OF DISEASES OF CHILDREN, August, 1920, p. 127, an erroneous legend was attached to Figure 3: "The degree of development of lymph vessels and blood vessels in early months of life." As stated in the text, this figure is taken from the paper by Holland and Meyer, *München. med. Wchnschr.,* **66**:1191, 1919. The manuscript did not contain this legend, and this figure represents capillaries.

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